#31
attachments

EXHIBIT A

Curriculum Vitae of Daniel C. Maneval, Ph.D.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Pag 2.
Photocopy this pag or follow this format for each person.

NAME	POSITION TITLE
Daniel C. Maneval	Group Director, Pharmacology

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Boston University, Boston, MA	B.S.	1982	Biomedical Engineering
University of Southern California, Los Angeles, CA	M.S.	1984	Biomedical Engineering
University of Southern California, Los Angeles, CA	Ph.D.	1989	Biomedical Engineering

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds three pages, select the most pertinent publications.

Research and Professional Experience:

1985 -- 1988	Research Assistant, Department of Biomedical Engineering, University of Southern California
1988 -- 1989	Assistant Research Professor, Biomedical Modeling Laboratory, Center for Pediatric, Pharmacokinetics and Therapeutics, Univ. of Tennessee, Memphis; and Postdoctoral Fellow, Pharmacokinetics Laborator St. Jude Children's Research Hospital
1989 -- 1992	Scientist, Pharmacokinetics Group, Genentech, Inc.
1993 – 1994	Senior Scientist, Pharmacology, Canji, Inc.
1994 -- 1996	Director, Pharmacology, Canji, Inc.
1996 – present	Group Director, Pharmacology, Canji/Schering-Plough

Relevant Publications:

Singh M, Horne C, Maneval D, Amartey J, and Brechner R: Non-Uniform Attenuation and Scatter Correction in SPECT. *IEEE Transactions on Nuclear Science* NS-35:767-771, 1988.

D'Argenio DZ and Maneval DC: Estimation Approaches for Modeling Sparse Data Systems. In Cobelli C and Mariani L, editors, *Modelling and Control in Biomedical Systems*, Venice, Italy, 61-67, 1988.

Maneval DC, D'Argenio DZ, and Wolf W: A Kinetic Model for Tc-99m DMSA in the Rat. *The European Journal of Nuclear Medicine* 16:29-34, 1990.

Maneval DC, Magill HL, Cypess AM, and Rodman JH: Measurement of Skin to Kidney Center Distance in Children: Implications for Quantitative Renography. *The Journal of Nuclear Medicine 31:287*-291, 1990 .

Houghton JA, Williams LG, de Graaf SS, Chesire PJ, Rodman JH, Maneval DC, Wainer IW, Jadaud P, and Houghton PJ: Relationship Between Dose Rate of [6RS]Leucovorin Administration, Plasma Concentration of Reduced Folates and Pools of 5,10-methylenetetrahydrofolates and Tetrahydrofolates in Human Colon Adenocarcinoma Xenografts. *Cancer Research* 50:3493-3502, 1990.

Shepard HM, Lewis GD, Sarup JS, Fendly BM, Maneval DC, Mordenti J, Figari I, Kotts CE, Palladino MA, Ullrich A, and Slamon D: Monoclonal Antibody Therapy of Human Cancer: Taking the HER2 Protooncogene to the Clinic. *Journal of Clinical Immunology* 11(3):117-127, 1991.

Park JW, Stagg R, Lewis GD, Carter P, Maneval D, Slamon DJ, Jaffe H, and Shepard HM: Anti-p185HER2 monoclonal antibodies: Biological properties and potential for immunotherapy. In *Genes, Oncogenes, and Hormones: Advances in Cellular and Molecular Biology of Breast Cancer*. Dickson RB and Lippman ME (eds), Kluwer Academic Publishers, Boston MA, pp. 193-211, 1991.

DeSantes K, Slamon D, Anderson SK, Shepard M, Fendly B, Maneval D, Press O: Radiolabeled Antibody Targeting of the HER-2/*neu* Oncoprotein. *Cancer Research* 52:1916-1923, 1992.

Rodman JH, Maneval DC, Magill HL, and Sunderland M: Measurement of Tc-99m DTPA Serum Clearance for the Estimation of GFR in Pediatric `Cancer Patients. *Pharmacotherapy*, 13:10-16, 1992.

Rodrigues ML, Snedecor B, Chen C, Wong WLT, Garg S, Blank GS, Maneval D, and Carter P: Engineering Fab' Fragments for Efficient F(ab)'2 formation in *Escherichia coli* and for Improved In Vivo Stability. *Journal of Immunology* 151:6954-6961, 1993.

Wills K, Maneval DC, Menzel P, Harris MP, Sutjipto S, Vaillancourt M, Huang WM, Johnson DE, Anderson SC, Wen SF, Bookstein R, Shepard HM, Gregory RJ. Development and Characterization of Recombinant Adenoviruses Encoding Human p53 for Gene Therapy of Cancer. *Human Gene Therapy* 5:1079-1088, 1994.

Shalaby MF, Carter P, Maneval D, Giltinan D, and Kotts C. Bispecific HER2xCD3 Antibodies Enhance T-Cell Cytotoxicity in Vitro and Localize to HER2 Overexpressing Xenografts in Nude Mice. *Clinical Immunology and Immunopathology* 74:185-192, 1995.

Antelman D, Machemer T, Huyghe B, Shepard HM, Maneval D, Johnson DE. Inhibition of tumor cell proliferation in vitro and in vivo by exogenous p110RB, the retinoblastoma tumor suppressor protein. *Oncogene* 10:697-704, 1995.

Pagliaro LC, Antelman D, Johnson DE, Machemer T, McCulloch EA, Freireich EJ, Stass SA, Shepard HM, Maneval D, and Gutterman JU. Recombinant human retinoblastoma protein inhibits cancer cell growth. *Cell Growth and Differentiation* 6:673-680, 1995.

Bass C, Cabrera G, Elgavish A, Robert B, Siegal G, Anderson SC, Maneval DC, and Curiel DT. Recombinant adenovirus-mediated gene transfer to genito-urinary epithelium in vitro and in vivo. *Cancer Gene Therapy* 2:97-104, 1995.

Wills KN, Huang W-M, Harris MP, Machemer T, Maneval DC, and Gregory RJ. Gene therapy for hepatocellular carcinoma: Chemosensitivity conferred by adenovirus-mediated transfer of the HSV-1 thymidine kinase gene. *Cancer Gene Therapy* 2:191-197, 1995.

Harris MP, Sutjipto S, Wills KN, Hancock W, Cornell D, Johnson DE, Gregory RJ, Shepard HM, and Maneval DC. Adenovirus-mediated p53 gene transfer inhibits growth of human tumor cells expressing mutant p53 protein. *Cancer Gene Therapy* 3:121-130, 1996.

Bookstein R, Demers W, Gregory R, Maneval D, Park J, and Wills K. p53 gene therapy in vivo of hepatocellular and liver metastatic colorectal cancer. *Seminars in Oncology* 23:1-13, 1996.

Mujoo K, Maneval DC, Anderson SC, and Gutterman JU. Adenoviral-mediated p53 tumor suppressor gene therapy of human ovarian carcinoma. *Oncogene* 12:1617-1623, 1996.

Watanabe T, Kuszynski C, Kazuhiko I, Heimann DG, Shepard HM, Yasui Y, Maneval DC, and Talmadge JE. Gene transfer into human bone marrow hematopoietic cells mediated by adenovirus vectors. *Blood* 87:5032-5039, 1996.

Kock H, Harris MP, Anderson SC, Machemer T, Hancock W, Sutjipto S, Wills KN, Gregory RJ, Shepard HM, Westphal M, and Maneval DC. Adenovirus-mediated p53 gene transfer suppresses growth of human glioblastoma cells in vitro and in vivo. *International Journal of Cancer* 67:808-815, 1996.

Nielsen, L.L., J. Dell, E. Maxwell, L. Armstrong, D. Maneval, and J. Catino. Efficacy of p53 adenovirus-mediated gene therapy against human breast cancer xenografts. *Cancer Gene Therapy* 4: 129-138 1997.

Linke SP, Harris MP, Neugebauer SE, Clarkin KC, Shepard HM, Maneval DC, and Wahl GM. p53-mediated accumulation of hypophosphorylated pRb after the G1 restriction point fails to halt cell cycle progression. *Oncogene.* 15:337-345, 1997.

Nielsen LL and Maneval DC. p53 tumor suppressor gene therapy for cancer. *Cancer Gene Therapy* 5:52-63, 1998.

Watanabe T, Kelsey L, Ageitos A, Kuszynski C, Ino K, Hiemann DG, Varney MT, Shepard HM, Vaillancourt MT, Maneval DC and Talmadge JE. Enhancement of adenovirus-mediated gene transfer to human bone marrow cells. *Leukemia and Lymphoma* 29:439-51, 1998.

Anderson SC, Johnson DE, Harris MP, Engler H, Hancock W, Huang WM, Wills KN, Gregory RJ, Sutjipto S, Wen SF, Lofgren S, Shepard HM and Maneval DC. p53 gene therapy in a rat model of hepatocellular carcinoma: Intra-arterial delivery of a recombinant adenovirus. *Clinical Cancer Research* 4:1649-59, 1998.

Demers GW, Harris MP, Wen SF, Engler HE, Machemer T, and Maneval DC. A recombinant adenoviral vector expressing full length human retinoblastoma susceptibility gene inhibits human tumor cell growth. *Cancer Gene Therapy* 5:207-214, 1998

Pietras RJ, Pegram MD, Finn RS, Maneval D, Slamon DJ. Remission of human breast cancer xenografts on therapy with humanized monoclonal antibody to HER-2 receptor and DNA-reactive drugs. *Oncogene* 17:2235-2249, 1998.

Mujoo K, Catino JC, Maneval DC, Gutterman JU. p53 induced growth inhibition and apoptosis with p53-adenoviral construct in human ovarian cancer. *Int J Gynecol Cancer* 8:233-241, 1998

Hirai M, Kelsey LS, Maneval DC, Vaillancourt M, Talmadge JE. Adenovirus p53 purging for human breast cancer cell products. *Acta Hematologica* 101:97-105, 1999.

Engler H, Anderson SC, Machemer TR, Philopena JM, Connor RJ, Wen SF, Maneval DC. Ethanol improves adenovirus-mediated gene transfer and expression to the bladder epithelium of rodents. *Urology* 53, 1049-1053, 1999.

Hirai M, Kelsey LS, Watanabe T, Maneval DC, Vaillancourt MT, Talmadge JE. Purging of human breast cancer cells from stem cell products with an adenovirus containing p53. *Cancer Gene Therapy* 7:197-206, 2000.

Connor RJ, Engler H, Machemer T, Philopena JM, Horn MT, Sutjipto S, Maneval DC, Youngster S, Chan TM, Bausch J, McAuliffe JP, Hindsgaul O, Nagabhushan TL. Identification of polyamines that enhance adenovirus-mediated gene expression in the urothelium. *Gene Therapy* 8:41-48, 2001.

Rahman A, Tsai V, Goudreau A, Shinoda JY, Wen SF, Ramachandra M, Ralston R, Maneval D, LaFace D, Shabram P. Specific depletion of human anti-adenovirus antibodies facilitates transduction in an in vivo model for systemic gene therapy. *Molecular Therapy* 3:768-778, 2001.

Ahm d ICM, Johnson DE, Demers GW, Engler H, Howe JA, Wills KN, Wen SF, Shinoda J, Beltran J, Nodelman M, Machemer T, Maneval DC, Nagabhushan TL, Sugarman BJ. Interferon alpha2b gene delivery using adenoviral vector causes inhibition of tumor growth in xenograft models from a variety of cancers. *Cancer Gene Therapy* 8:788-95, 2001.

Hirai M, LaFace D, Robinson S, Kelsey L, Johnson R, Wen SF, Warkentin P, Mills K, Vaillancourt M, Chavez J, Leutzinger C, Sumegi J, Neugebauer S, Lehman J, Talmadge C, Maneval D, Talmadge J. Ex vivo purging by adenoviral p53 gene therapy does not affect NOD-SCID repopulating activity of human CD34+ cells. Cancer Gene Therapy 8:936-47, 2001.

Kuball J, Wen SF, Leissner J, Atkins D, Meinhardt P, Quijano E, Engler H, Hutchins B, Maneval DC, Grace MJ, Fritz MA, Storkel S, Thuroff JW, Huber C, Schuler M. Successful adenovirus-mediated wild-type p53 gene transfer in patients with bladder cancer by intravesical vector instillation. *J Clin Oncol* 20:957-65, 2002.

Abe T, Wakimoto H, Bookstein R, Maneval DC, Chiocca EA, Basilion JP. Intra-arterial delivery of p53-containing adenoviral vector into experimental brain tumors. *Cancer Gene Therapy* 9:228-35, 2002.

Demers GW, Sugarman BJ, Beltran JC, Westreich LN, Ahmed CM, Lau JY, Hong Z, Lanford RE, Maneval DC. Interferon-alpha2b secretion by adenovirus-mediated gene delivery in rat, rabbit, and chimpanzee results in similar pharmacokinetic profiles. *Toxicol Appl Pharmacol* 180:36-42, 2002.

Perkins TW, Faha B, Ni M, Kiland JA, Poulsen GL, Antelman D, Atencio I, Shinoda J, Sinha D, Brumback L, Maneval D, Kaufman PL, Nickells RW. Adenovirus-mediated gene therapy using human p21WAF-1/Cip-1 to prevent wound healing in a rabbit model of glaucoma filtration surgery. *Arch Ophthalmol* 20:941-9, 2002.

HUMAN GENE TRANSFER PROTOCOLS
Last updated: 02-28-03

EXHIBIT
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8810-001 (Closed) Gene Marking/Cancer
In Vitro/Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *The Treatment of Patients with Advanced Cancer Using Cyclophosphamide, Interleukin-2 and Tumor Infiltrating Lymphocytes.*

*RAC Recommends Approval: 10-3-88/NIH Approval: 3-2-89

9007-002 (Closed) Gene Therapy/Phase I/Monogenic Disease/Severe Combined Immune Deficiency due to Adenosine Deaminase Deficiency
In Vitro/Autologous Peripheral Blood Cells/CD34+ Autologous Peripheral Blood Cells/Cord Blood/Placenta Cells/Retrovirus/Adenosine Deaminase cDNA/Neomycin Phosphotransferase cDNA/Intravenous

Blaese, R. Michael; National Institutes of Health, Bethesda, Maryland; *Treatment of Severe Combined Immune Deficiency (SCID) due to Adenosine Deaminase (ADA) Deficiency with Autologous Lymphocytes Transduced with the Human ADA Gene: An Experimental Study.*

*RAC Recommends Approval: 7-31-90/NIH Approval: 9-6-90

9007-003 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Tumor Infiltrating Lymphocytes/Retrovirus/Cytokine/Tumor Necrosis Factor cDNA/Neomycin Phosphotransferase cDNA/Intravenous

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Gene Therapy of Patients with Advanced Cancer Using Tumor Infiltrating Lymphocytes Transduced with the Gene Coding for Tumor Necrosis Factor.*

*RAC Recommends Approval: 7-31-90/NIH Approval: 9-6-90

9102-004 (Closed) Gene Marking/Cancer/Acute Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Mirro, Joseph; Hurwitz, Craig; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *Autologous Bone Marrow Transplant for Children with Acute Myelogenous Leukemia in First Complete Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse.*

*RAC Recommends Approval: 2-4-91/NIH Approval: 7-12-91
Closed: 1-21-93

9105-005 (Closed) Gene Marking/Cancer/Neuroblastoma
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Mirro, Joseph; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Phase I/II Trial of High Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Stage D Neuroblastoma in First Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse.*

*RAC Recommends Approval: 5-31-91/NIH Approval: 7-12-91
Closed: 9-1-92

9105-006 (Closed) Gene Marking/Cancer/Neuroblastoma
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Mirro, Joseph; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Phase II Trial of High-Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Relapse/Refractory Neuroblastoma Without Apparent Bone Marrow Involvement.*

*RAC Recommends Approval: 5-31-91/NIH Approval: 7-12-91
Closed: 4-9-93

9105-007 (Closed) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; M.D. Anderson Cancer Research Center, Houston, Texas; *Autologous Bone Marrow Transplantation for Chronic Myelogenous Leukemia in which Retroviral Markers are Used to Discriminate between Relapse which Arises from Systemic Disease Remaining after Preparative Therapy Versus Relapse due to Residual Leukemic Cells in Autologous Marrow: A Pilot Trial.*

*RAC Recommends Approval: 5-31-91/NIH Approval: 7-12-91
Closed: 6-1-93
Closed: 4-9-93

9105-008 (Closed) Gene Marking/Acute Hepatic Failure
In Vitro/Autologous Hepatocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intrahepatic

Ledley, Fred D.; Woo, Savio; Ferry, George; and Hartwell, Whisennand; Baylor College of Medicine, Houston, Texas; *Hepatocellular Transplantation in Acute Hepatic Failure and Targeting Genetic Markers to Hepatic Cells.*

*RAC Recommends Approval: 5-30-91/NIH Approval: 7-12-91
Closed: Protocol Never Initiated

9105-009 (Closed) Gene Marking/Cancer/Melanoma
In Vitro/Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Lotze, Michael T.; University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; *The Administration of Interleukin-2 and Tumor Infiltrating Lymphocytes to Patients with Melanoma.*

*RAC Recommends Approval: 5-30-91/NIH Approval: 1-17-92
Closed: 4-95

9110-010 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Renal Cell/Colon/Breast/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Tumor Necrosis Factor cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Tumor Necrosis Factor (TNF).*

*RAC Recommends Approval: 10-7-91/NIH Approval: 10-15-91

9110-011 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Renal Cell/Colon/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Interleukin-2 (IL-2).*

*RAC Recommends Approval: 10-7-91/NIH Approval: 10-15-91

9110-012 (Closed) Gene Therapy/Phase I/Monogenic Disease/Familial Hypercholesterolemia
In Vitro/Low Density Lipoprotein Receptor cDNA/Intrahepatic/Portal Vein Catheter

Wilson, James M.; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Ex Vivo Gene Therapy of Familial Hypercholesterolemia.*

*RAC Recommends Approval: 10-8-91/NIH Approval: 11-14-91
Closed: 3-11-94

9202-013 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Adenocarcinoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DC-Chol/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection/Catheter Delivery to Pulmonary Nodules

Nabel, Gary J.; University of Michigan, Ann Arbor, Michigan; *Immunotherapy of Malignancy by In Vivo Gene Transfer into Tumors.*

*RAC Recommends Approval: 2-10-92/NIH Approval: 4-17-92
Closed: 11-19-92 (Replaced by Protocol #9306-045)

9202-014 (Closed) Gene Marking/Cancer/Acute Myelogenous Leukemia/Acute Lymphocytic Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant
Cornetta, Kenneth; Indiana University, Indianapolis, Indiana; *Retroviral-Mediated Gene Transfer of Bone Marrow Cells during Autologous Bone Marrow Transplantation for Acute Leukemia.*

*RAC Recommends Approval: 2-11-92/NIH Approval: 4-17-92
Closed 5-1-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9202-015 (Closed) Gene Marking/Cancer/Melanoma/Renal Cell
In Vitro/CD4+ Autologous Peripheral Blood Lymphocytes/CD8+ Autologous Peripheral Blood Lymphocytes/CD4+ Autologous Tumor Infiltrating Lymphocytes/CD8+ Autologous Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Economou, James S. and Belldegrun, Arie; University of California at Los Angeles, Los Angeles, California; *The Treatment of Patients with Metastatic Melanoma and Renal Cell Cancer Using In Vitro Expanded and Genetically-Engineered (Neomycin Phosphotransferase) Bulk, CD8 (+) and/or CD4(+) Tumor Infiltrating Lymphocytes and Bulk, CD8(+) and/or CD4(+) Peripheral Blood Leukocytes in Combination with Recombinant Interleukin-2 Alone, or with Recombinant Interleukin-2 and Recombinant Alpha Interferon.*

*RAC Recommends Approval: 2-11-92/NIH Approval: 4-17-92
Closed: 6-94

9202-016 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraperitoneal Administration

Freeman, Scott M.; Tulane University Medical Center, New Orleans, Louisiana; *Gene Transfer for the Treatment of Cancer.*

*RAC Recommends Approval: 2-10-92/NIH Approval: 2-5-93

9202-017 (Open) Gene Therapy/Infectious Disease/Human Immunodeficiency Virus
In Vitro/CD8+ Allogeneic Cytotoxic T Lymphocytes/CD8+ Syngeneic Cytotoxic T Lymphocytes/Retrovirus/Hygromycin Phosphotransferase/Herpes Simplex Virus Thymidine Kinase cDNA/Intravenous

Greenberg, Philip D. and Riddell, Stanley; Fred Hutchinson Cancer Research Center, University of Washington, Seattle; *Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy Using Genetically Modified CD8+ HIV-Specific T Cells in HIV Seropositive Individuals.*

*RAC Recommends Approval: 2-11-92/NIH Approval: 4-17-92

9206-018 (Closed) Gene Therapy/Phase I/Cancer/Relapsed-Refractory Neuroblastoma/Immunotherapy
In Vitro/Autologous Neuroblastoma Cells/Allogeneic Partially HLA-Matched/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Brenner, Malcolm K.; Furman, Wayne; Santana, Victor; Bowman, Laura; and Meyer, William; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Cytokine-Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma.*

*RAC Recommends Approval: 6-1-92/NIH Approval: 8-14-92

9206-019 (Closed) Gene Therapy/Phase I/Cancer/Brain/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Stereotactic Injection

Oldfield, Edward; National Institutes of Health, Bethesda, Maryland; *Gene Therapy for the Treatment of Brain Tumors Using Intra-Tumoral Transduction with the Thymidine Kinase Gene and Intravenous Ganciclovir.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 6-1-92/NIH Approval: 8-14-92
Closed: 12-94

9206-020 (Closed) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; MD Anderson Cancer Center, Houston, Texas; *Use of Two Retroviral Markers to Test Relative Contribution of Marrow and Peripheral Blood Autologous Cells to Recovery After Preparative Therapy.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92
Closed: 2-13-96

9206-021 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Partially HLA-Matched/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Gansbacher, Bernd; Houghton, Alan; and Livingston, Philip; Memorial Sloan Kettering Cancer Center, New York, New York; *Immunization with HLA-A2 matched Allogeneic Melanoma Cells that Secrete Interleukin-2 in Patients with Metastatic Melanoma.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92
Closed: 10-19-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9206-022 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vitro/Allogeneic Partially HLA-Matched/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Gansbacher, Bernd; Motzer, Robert; Houghton, Alan; and Bander, Neil; Memorial Sloan Kettering Cancer Center, New York, New York; *Immunization with Interleukin-2 Secreting Allogeneic HLA-A2 Matched Renal Cell Carcinoma Cells in Patients with Advanced Renal Cell Carcinoma.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92

9206-023 (Closed) Gene Marking/Cancer/Multiple Myeloma
In Vitro/CD34+ Autologous Peripheral Blood Cells/Intravenous/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; *Retroviral-Mediated Gene Transfer of Bone Marrow and Peripheral Blood Stem Cells During Autologous Bone Marrow Transplantation for Multiple Myeloma.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92

9206-024 (Closed) Gene Marking/Cancer/Breast
In Vitro/CD34+ Autologous Peripheral Blood Cells/Intravenous/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; *Retroviral-Mediated Gene Transfer of Bone Marrow and Peripheral Blood Stem Cells During Autologous Bone Marrow Transplantation for Metastatic Breast Cancer.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92

9206-025 (Closed) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/CD34+ Autologous Peripheral Blood Cells/Intravenous/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; *Retroviral-Mediated Gene Transfer of Bone Marrow and Peripheral Blood Stem Cells During Autologous Bone Marrow Transplantation for Chronic Myelogenous Leukemia.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92

9209-026 (Closed) Gene Marking/Infectious Disease/Human Immunodeficiency Virus
In Vitro/Syngeneic Peripheral Blood Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Tavel, Jorge; National Institutes of Health, Bethesda, Maryland; *A Study of the Safety and Survival of the Adoptive Transfer of Genetically Marked Syngeneic Lymphocytes in HIV Infected Identical Twins.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 9-3-93
Closed to new enrollment. Individuals will be followed, long-term, in a new protocol (that does not involve administration of recombinant DNA): 1-17-02

9209-027 (Closed) Gene Marking/Cancer
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Schuening, Friedrich G.; Miller, A. Dusty; and Kiem, Hans-Peter; Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; *Study on Contribution of Genetically Marked Peripheral Blood Repopulating Cells to Hematopoietic Reconstitution after Transplantation.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 2-5-93
Closed: 4-29-97

9209-028 (Closed) Gene Marking/Cancer/Lymphoid Malignancies/
In Vitro/G-CSF Mobilized Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Schuening, Friedrich G.; Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; *Evaluation of the Use of Recombinant Human G-CSF Stimulated Peripheral Blood Progenitor Cell Supplementation in Autologous Bone Marrow Transplantation in Patients with Lymphoid Malignancies.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 2-5-93
Closed: 2-25-94 (Merged with protocol # 9209-027)

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9209-029 (Closed) Gene Marking/Cancer/
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Schuening, Friedrich G.; Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; *A Trial of G-CSF Stimulated Peripheral Blood Stem Cells for Engraftment in Identical Twins.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 2-5-93
Closed: Protocol Never Initiated

9209-030 (Open) Gene Marking/Cancer/Chronic Lymphocytic Leukemia/Follicular Non-hodgkins Lymphoma
In Vitro/Autologous Bone Marrow Cells/Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; University of Texas MD Anderson Cancer Center, Houston, Texas; *Use of Retroviral Markers to Identify Efficacy of Purging and Origin of Relapse Following Autologous Bone Marrow and Peripheral Blood Cell Transplantation in Indolent B Cell Neoplasms (Follicular Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia) Patients.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 12-2-93

9403-031 (Open) Gene Therapy/Phase I/Cancer/Non-small Cell Lung Cancer/Antisense/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Retrovirus/p53 cDNA/kras Antisense/Intratumoral/Bronchoscope

Roth, Jack A.; The University of Texas MD Anderson Cancer Center, Houston, Texas; and Garver, Robert I., Jr.; University of Alabama at Birmingham, Birmingham, AL; *Clinical Protocol for Modification of Oncogene and Tumor Suppressor Gene Expression in Non-Small Cell Lung Cancer (NSCLC).*

*RAC Recommends Approval: 3-4-94/NIH Approval: 1-4-95

9209-032 (Closed) Gene Marking/Cancer/Neuroblastoma
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Phase II Trial of the Baxter Neuroblastoma Bone Marrow Purging System Using Gene Marking to Assess Efficacy.*

*RAC Recommends Approval: 9-15-92/NIH Approval: 2-5-93

9209-033 (Open) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vitro/Autologous Fibroblasts/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Retrovirus/Cytokine/Interleukin-4 cDNA/Subcutaneous Injection

Lotze, Michael T. and Rubin, Joshua T.; University of Pittsburgh, Pittsburgh, Pennsylvania; *Gene Therapy of Cancer: A Pilot Study of IL-4 Gene Modified Antitumor Vaccines.*

*RAC Recommends Approval: 9-15-92/NIH Approval: 2-5-93

9212-034 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Crystal, Ronald G.; Rockefeller University Hospital, New York, New York; *A Phase I Study, in Cystic Fibrosis Patients, of the Safety, Toxicity, and Biological Efficacy of a Single Administration of a Replication Deficient, Recombinant Adenovirus Carrying the cDNA of the Normal Human Cystic Fibrosis Transmembrane Conductance Regulator Gene in the Lung.*

*RAC Recommends Approval: 12-3-92/NIH Approval: 4-16-93
Protocol closed, IND inactive: 5-30-00

9212-035 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/E2a Temperature Sensitive Mutant/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Wilson, James M., University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; Simon, Richard H., University of Michigan Medical Center, Ann Arbor, Michigan; McCoy, Karen, Cystic Fibrosis Center at Ohio State University; *Gene Therapy of Cystic Fibrosis Lung Diseases Using E1 Deleted Adenoviruses: A Phase I Trial.*

*RAC Recommends Approval: 12-3-92/NIH Approval: 8-26-93

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9212-036 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal

Welsh, Michael J.; Howard Hughes Medical Institute, Iowa City, Iowa; and Smith, Alan E.; Genzyme Corporation, Framingham, Massachusetts; *Cystic Fibrosis Gene Therapy Using an Adenovirus Vector: In Vivo Safety and Efficacy in Nasal Epithelium.* Sponsor: Genzyme Corporation

*RAC Recommends Approval: 12-4-92/NIH Approval: 4-16-93
Protocol ended in November 1993

9303-037 (Closed) Gene Therapy/Phase I/Cancer/Glioblastoma/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Van Gilder, John C.; University of Iowa, Iowa City, Iowa; Berger, Mitchell; University of California, San Francisco, California; Prados, Michael; University of Washington, Seattle, Washington; Warnick, Ronald; University of Cincinnati Medical Center, Cincinnati, Ohio; Schold, Clifford; University of Texas Southwestern Medical Center, Dallas, Texas; Fetell, Michael; Columbia Presbyterian Medical Center, New York, New York; Schramm, Johannes; Neurochirurgische Universitatsklinik, Bonn, Germany; Westphal, Manfred; University Clinic Eppendorf, Hamburg, Germany; Tonn, Jorg-Christian; University Kliniken, Wurzburg, Germany; Moumdjian, Robert; Notre-Dame Hospital, Montreal, Quebec, Canada; Shaffrey, Mark; University of Virginia, Charlottesville, Virginia; Asher, Anthony; Charlotte Neurological Associates and Presbyterian Hospital, Charlotte, North Carolina; Epstein, Mel; Brown University, Providence, Rhode Island; Schmitz-Schackert, Gabriele Anna Maria; University Klinikum Karl-Gustav-Carus, Dresden, Germany; Mendez, Ivar; Victoria General Hospital, Nova Scotia, Canada; Bernstein, Mark; The Toronto Hospital, Toronto, Ontario, Canada; *Gene Therapy for the Treatment of Recurrent Glioblastoma Multiforme with In Vivo Tumor Transduction with the Herpes Simplex Thymidine Kinase Gene/Ganciclovir System.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 3-1-93/NIH Approval: 4-16-93

9303-038 (Open) Gene Marking/Cancer/Leukemia/Non-malignant Disorders
In Vitro/Epstein-Barr Virus Specific Allogeneic Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Heslop, Helen E.; Brenner, Malcolm K.; and Rooney, Cliona; St. Jude Children's Research Hospital, Memphis, Tennessee; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes to Recipients of Mismatched-Related or Phenotypically Similar Unrelated Donor Marrow Grafts.*

*RAC Recommends Approval: 3-2-93/NIH Approval: 4-16-93

9303-039 (Closed) Gene Marking/Cancer/Acute Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Krance, Robert; Heslop, Helen E.; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *Assessment of the Efficacy of Purging by Using Gene-Marked Autologous Marrow Transplantation for Children with Acute Myelogenous Leukemia in First Complete Remission.*

*RAC Recommends Approval: 3-2-93/NIH Approval: 4-16-93

9303-040 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Subcutaneous Injection

Simons, Jonathan; Johns Hopkins Oncology Center, Baltimore, Maryland; *Phase I Study of Non-Replicating Autologous Tumor Cell Injections Using Cells Prepared With or Without Granulocyte-Macrophage Colony Stimulating Factor Gene Transduction in Patients with Metastatic Renal Cell Carcinoma.*

*RAC Recommends Approval: 3-1-93/NIH Approval: 12-2-93
Study closed, long-term follow-up continues: 7-16-01

9303-041 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Wilmott, Robert W. and Whitsett, Jeffrey; Children's Hospital Medical Center, Cincinnati, Ohio; and Trapnell, Bruce; Genetic Therapy, Inc., Gaithersburg, Maryland; *A Phase I Study of Gene Therapy of Cystic Fibrosis Utilizing a Replication Deficient Recombinant Adenovirus Vector to Deliver the Human Cystic Fibrosis Transmembrane Conductance Regulator cDNA to the Airways.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 3-2-93/NIH Approval: 4-16-93
Closed: 4-28-97 (IND Withdrawn)

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9303-042 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator CDNA/Intranasal

Boucher, Richard C. and Knowles, Michael R.; University of North Carolina, Chapel Hill, North Carolina; *Gene Therapy for Cystic Fibrosis Using E1 Deleted Adenovirus: A Phase I Trial in the Nasal Cavity.*

*RAC Recommends Approval: 3-2-93/NIH Approval: 10-7-93
Closed: 10-94

9306-043 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Gamma Interferon cDNA/Subcutaneous Injection

Seigler, Hilliard F.; Duke University Medical Center, Durham, North Carolina; and Merritt, James A.; Viagene, Inc., San Diego, California; *A Phase I Trial of Human Gamma Interferon-Transduced Autologous Tumor Cells in Patients With Disseminated Malignant Melanoma.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93

9306-044 (Closed) Gene Therapy/Phase I/Cancer/Ovarian/Chemoprotection
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; Kavanagh, John; and Champlin, Richard; University of Texas MD Anderson Cancer Center, Houston, Texas; *Use of Safety-Modified Retroviruses to Introduce Chemotherapy Resistance Sequences into Normal Hematopoietic Cells for Chemoprotection During the Therapy of Ovarian Cancer: A Pilot Trial.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 12-2-93

9306-045 (Closed) Gene Therapy/Phase I/Cancer/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection/Catheter Delivery to Pulmonary Nodules

Nabel, Gary J.; University of Michigan Medical Center, Ann Arbor, Michigan; *Immunotherapy for Cancer by Direct Gene Transfer into Tumors.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93

9306-046 (Closed) Gene Therapy/Phase I/Monogenic Disease/Gaucher Disease
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Glucocerebrosidase cDNA/Bone Marrow Transplant

Barranger, John A.; University of Pittsburgh, Pittsburgh, Pennsylvania; *Gene Therapy for Gaucher Disease: Ex Vivo Gene Transfer and Autologous Transplantation of CD34(+) Cells.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93

9306-047 (Closed) Gene Therapy/Phase I/Monogenic Disease/Gaucher Disease
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Glucocerebrosidase cDNA/Bone Marrow Transplant

Karlsson, Stefan and Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; and Kohn, Donald B.; Childrens Hospital Los Angeles, Los Angeles, California; *Retroviral Mediated Transfer of the cDNA for Human Glucocerebrosidase into Hematopoietic Stem Cells of Patients with Gaucher Disease.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93
Closed: 4-30-97 (IND Withdrawn)

9306-048 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Galpin, Jeffrey E.; University of Southern California; Casciato, Dennis A.; Shared Medical Research Foundation, Tarzana, California; and Merritt, James A.; Viagene, Inc., San Diego, California; *A Preliminary Study to Evaluate the Safety and Biologic Effects of Murine Retroviral Vector Encoding HIV-1 Genes [HIV-IT(V)] in Asymptomatic Subjects Infected with HIV-1.* Sponsor: Chiron Corporation

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93
Closed: 9-8-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9306-049 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense In Vitro/CD4+ Autologous Peripheral Blood Cells/Retrovirus/Particle Mediated Gene Transfer (Accell®)/RSV-tar/Rev M10/Intravenous

Nabel, Gary J.; University of Michigan Medical Center, Ann Arbor, Michigan; *A Molecular Genetic Intervention for AIDS - Effects of a Transdominant Negative Form of Rev.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93

IND terminated: 3-13-00

9306-050 (Open) Gene Therapy/Phase I/Cancer/Astrocytoma/Pro-Drug In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Ommaya Injection

Raffel, Corey; Mayo Clinic, Rochester, Minnesota; Villablanca, Judith; Childrens Hospital Los Angeles, Los Angeles, California; Packer, Roger, Childrens National Medical Center, Washington, DC; Tonn, Jorg-Christian, Neurochirurgische Klinik und Poliklinik, Universitats-Klinikin, Wurzburg, Germany; and Burdach, Stefan; University Center for Paediatrics, Heinrich-Heine Universitat, Dusseldorf, Germany; *Gene Therapy for the Treatment of Recurrent Pediatric Malignant Astrocytomas with In Vivo Tumor Transduction with the Herpes Simplex Thymidine Kinase Gene.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 6-8-93/NIH Approval: 9-3-93

9306-051 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Brain/Chemoprotection In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Bone Marrow Transplant

Hesdorffer, Charles and Antman, Karen; Columbia University College of Physicians and Surgeons, New York, New York; *Human MDR Gene Transfer in Patients with Advanced Cancer.*

*RAC Recommends Approval: 6-8-93/NIH Approval: 9-3-93

9306-052 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Antisense In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin (Gibco BRL)/Insulin-like Growth Factor Antisense/Subcutaneous Injection

Ilan, Joseph; Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio; *Gene Therapy for Human Brain Tumors Using Episome-Based Antisense cDNA Transcription of Insulin-Like Growth Factor I.*

*RAC Recommends Approval: 6-8-93/NIH Approval: 12-2-93

9309-053 (Open) Gene Therapy/Phase I/Cancer/Small Cell Lung Cancer/Immunotherapy In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin (Gibco BRL)/Cytokine/Interleukin-2 cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Podack, Eckhard R.; Sridhar, Kasi; University of Miami; and Savaraj, Niramol; Miami Veterans Administration Hospital, Miami, Florida; *Phase I Study of Transfected Cancer Cells Expressing the Interleukin-2 Gene Product in Limited Stage Small Cell Lung Cancer.*

*RAC Recommends Approval: 9-9-93/NIH Approval: 12-2-93

9309-054 (Open) Gene Therapy/Phase I/Cancer/Breast/Chemoprotection In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Intravenous

O'Shaughnessy, Joyce; Kentuckiana Medical Oncology Association, Louisville, Kentucky; *Retroviral Mediated Transfer of the Human Multi-Drug Resistance Gene (MDR-1) into Hematopoietic Stem Cells During Autologous Transplantation after Intensive Chemotherapy for Breast Cancer.*

*RAC Recommends Approval: 9-9-93/NIH Approval: 10-7-93

9309-055 (Open) Gene Therapy/Phase I/Cancer/Brain Tumors/Pro-Drug In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Kun, Larry E.; Sanford, R. A.; Brenner, Malcolm K.; and Heideman, Richard L.; St. Jude Childrens Research Hospital, Memphis, Tennessee; and Oldfield, Edward H.; National Institutes of Health, Bethesda, Maryland; *Gene Therapy for Recurrent Pediatric Brain Tumors.* Sponsor: Genetic Therapy,
Inc./Novartis

*RAC Recommends Approval: 9-9-93/NIH Approval: 10-7-93

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9309-056 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Interleukin-2 cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Das Gupta, Tapas K. and Cohen, Edward P.; University of Illinois at Chicago, Chicago, Illinois; *Immunization of Malignant Melanoma Patients with Interleukin 2-Secreting Melanoma Cells Expressing Defined Allogeneic Histocompatibility Antigens.*

*RAC Recommends Approval: 9-10-93/NIH Approval: 4-19-94

9309-057 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition/Hairpin Ribozyme
In Vitro/CD4+ Peripheral Blood Cells/Retrovirus/Hairpin Ribozyme/Intravenous

Wong-Staal, Flossie; Poeschla, Eric; and Looney, David; University of California, San Diego, California; *A Phase I Clinical Trial to Evaluate the Safety and Effects in HIV-1 Infected Humans of Autologous Lymphocytes Transduced with a Ribozyme that Cleaves HIV-1 RNA.*

*RAC Recommends Approval: 9-10-93/NIH Approval: 10-25-94

9309-058 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Retrovirus/Interleukin-2 cDNA/Subcutaneous Injection

Economou, James S. and Glaspy, John A.; University of California Medical Center, Los Angeles, California; *Genetically Engineered Autologous Tumor Vaccines Producing Interleukin-2 for the Treatment of Metastatic Melanoma.*

*RAC Recommends Approval: 9-10-93/NIH Approval: 12-2-93

9312-059 (Closed) Gene Therapy/Phase I/Cancer/Leptomeningeal Carcinomatosis/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraventricular Injection/Subarachnoid Injection

Oldfield, Edward H. and Ram, Zvi; National Institutes of Health, Bethesda, Maryland; *Intrathecal Gene Therapy for the Treatment of Leptomeningeal Carcinomatosis.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 12-2-93/NIH Approval: 1-20-94
Closed: 1/95

9312-060 (Open) Gene Therapy/Phase I/Cancer/Colon/Immunotherapy
In Vitro/Autologous Fibroblasts/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Retrovirus/Interleukin-2 cDNA/Subcutaneous Injection

Sobol, Robert E. and Royston, Ivor; San Diego Regional Cancer Center, San Diego, California; *Injection of Colon Carcinoma Patients with Autologous Irradiated Tumor Cells and Fibroblasts Genetically Modified to Secrete Interleukin-2.*

*RAC Recommends Approval: 12-2-93/NIH Approval: 1-4-95

9312-061 (Closed) Gene Therapy/Phase I/Monogenic Disease/Gaucher Disease
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/Glucocerebrosidase cDNA/Intravenous

Schuening, Friedrich; Fred Hutchinson Cancer Research Center, Seattle, Washington; *Retrovirus-Mediated Transfer of the cDNA for Human Glucocerebrosidase into Peripheral Blood Repopulating Cells of Patients with Gaucher's Disease.*

*RAC Recommends Approval: 12-2-93/NIH Approval: 11-15-94
Closed: 4-29-97

9312-062 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Haubrich, Richard; University of California at San Diego Treatment Center, San Diego, California; and Merritt, James A.; Viagene, Inc., San Diego, California; *An Open Label, Phase I/II Clinical Trial to Evaluate the Safety and Biological Activity of HIV-IT(V) (HIV-1 IIIBenv/rev Retroviral Vector) in HIV-1 Infected Subjects.*

*RAC Recommends Approval: 12-3-93/NIH Approval: 4-19-94
Closed: 10-13-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9312-063 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin (Gibco BRL)/B7 (CD80) cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Sznol, Mario; National Institutes of Health, Frederick, Maryland; *A Phase I Trial of B7-Transfected Lethally Irradiated Allogeneic Melanoma Cell Lines to Induce Cell Mediated Immunity Against Tumor-Associated Antigens Presented by HLA-A2 or HLA-A1 in Patients with Stage IV Melanoma.*

*RAC Recommends Approval: 12-3-93/NIH Approval: 4-19-94

9312-064 (Closed) Gene Therapy/Phase I/Cancer/Colon/Hepatic Metastases/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Hepatic Injection

Rubin, Joseph; Mayo Clinic, Rochester, Minnesota; *Phase I Study of Immunotherapy of Advanced Colorectal Carcinoma by Direct Gene Transfer into Hepatic Metastases.* Sponsor: Vical, Incorporated

*RAC Recommends Approval: 12-3-93/NIH Approval: 4-19-94
Closed: 3-16-95 (Closed to accrual - maximum number of subjects entered)

9312-065 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Used in Combination with Anti-CD3 and Interleukin-2 Primed Autologous Lymph Node Cells to Prime Autologous Peripheral Blood Cells In Vitro/Retrovirus/GM-CSF cDNA/Intravenous

Chang, Alfred E.; University of Michigan, Ann Arbor, Michigan; *Adoptive Immunotherapy of Cancer with Activated Lymph Node Cells Primed In Vivo with Autologous Tumor Cells Transduced with the GM-CSF Gene.*

*RAC Recommends Approval: 12-3-93/NIH Approval: 8-23-94

9312-066 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Cationic Liposome Complex/DMRIE-DOPE/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal

Sorscher, Eric J. and Logan, James L.; University of Alabama, Birmingham, Alabama; *Gene Therapy for Cystic Fibrosis Using Cationic Liposome Mediated Gene Transfer: A Phase I Trial of Safety and Efficacy in the Nasal Airway.*

*RAC Recommends Approval: 12-3-93/NIH Approval: 1-4-95

9312-067 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Maxillary Sinus Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Maxillary Sinus Administration

Welsh, Michael J.; Howard Hughes Medical Institute, Iowa City, Iowa; *Adenovirus-Mediated Gene Transfer of CFTR to the Nasal Epithelium and Maxillary Sinus of Patients with Cystic Fibrosis.* Sponsor: Genzyme Corporation

*RAC Recommends Approval: 12-3-93/NIH Approval: 2-10-94
Protocol ended in May 1995

9403-068 (Closed) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Gamma Interferon cDNA/Subcutaneous Injection

Rosenblatt, Joseph; University of California, Los Angeles, California; Seeger, Robert; Childrens Hospital, Los Angeles, California; and Merritt, James A.; Viagene, Inc., San Diego, California; *A Phase I Study of Immunization with Gamma Interferon Transduced Neuroblastoma Cells.*

*RAC Recommends Approval: 3-3-94/NIH Approval: 10-25-94

9403-069 (Closed) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vitro/CD8+ Syngeneic Peripheral Blood Cells/Retrovirus/CD4-zeta Chimeric Receptor/Intravenous/Concurrent Interleukin-2 Therapy

Walker, Robert; National Institutes of Health, Bethesda, Maryland; *A Phase I/II Pilot Study of the Safety of the Adoptive Transfer of Syngeneic Gene-Modified Cytotoxic T-Lymphocytes in HIV-Infected Identical Twins.* Sponsor: NIH/Cell Genesys, Inc.

*RAC Recommends Approval: 3-3-94/NIH Approval: 8-23-94
Closed: 2-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9403-070 (Open) Gene Therapy/Phase I/Monogenic Disease/Alpha-1-Antitrypsin Deficiency
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Cationic Liposome Complex/DC-Chol-DOPE/Alpha-1 Antitrypsin cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Brigham, Kenneth; Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; *Expression of an Exogenously Administered Human Alpha-1-Antitrypsin Gene in the Respiratory Tract of Humans.* Sponsor: Gene Medicine, Inc.

*RAC Recommends Approval: 3-3-94/NIH Approval: 10-25-94

9403-071 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection

Vogelzang, Nicholas; the University of Chicago, Chicago, Illinois; *Phase I Study of Immunotherapy for Metastatic Renal Cell Carcinoma by Direct Gene Transfer into Metastatic Lesions.* Sponsor: Vical, Incorporated

*RAC Recommends Approval: 3-4-94/NIH Approval: 4-19-94
Closed: 4-5-95 (Closed to accrual - maximum number of subjects entered)

9403-072 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection

Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; and Akporiaye; Harris; Stopeck; Unger; and Warneke; University of Arizona, Tucson, Arizona; *Phase I Study of Immunotherapy of Malignant Melanoma by Direct Gene Transfer.* Sponsor: Vical, Incorporated

*RAC Recommends Approval: 3-4-94/NIH Approval: 4-19-94
Closed: 3-27-95 (Closed to accrual - maximum number of subjects entered)

-9406-073 (Open) Gene Therapy/Phase I/Colon/Immunotherapy
In Vivo/Autologous Tumor Cells/Plasmid DNA/Carcinoembryonic Antigen Plasmid Expression Vector/Kanamycin Resistance cDNA/Intratumoral/Direct Injection

Curiel, David; University of Alabama, Birmingham, Alabama; *Phase I Trial of a Polynucleotide Augmented Anti-Tumor Immunization to Human Carcinoembryonic Antigen in Patients with Metastatic Colorectal Cancer.*

*RAC Recommends Approval: 6-10-95/NIH Approval: 7-27-95

9406-074 (Closed) Gene Therapy/Phase I/Other/Rheumatoid Arthritis
In Vivo/Autologous Synovial Cells/Retrovirus/Interleukin-1 Receptor Antagonist Protein cDNA/Intrajoint/Metacarpal Phalangeal Joints

Evans, C. H. and Robbins, Paul; University of Pittsburgh, Pittsburgh, Pennsylvania; *Clinical Trial to Assess the Safety, Feasibility, and Efficacy of Transferring a Potentially Anti-arthritic Cytokine Gene to Human Joints with Rheumatoid Arthritis.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 7-27-95

9406-075 (Closed) Gene Marking/Cancer/Ovarian
In Vitro/Autologous Peripheral Blood Cells/Autologous Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intraperitoneal

Freedman, Ralph; MD Anderson Cancer Center, Houston, Texas; *Use of a Retroviral Vector to Study the Trafficking Patterns of Purified Ovarian TIL Populations Used in Intraperitoneal Adoptive Immunotherapy of Ovarian Cancer Patients: A Pilot Study.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 7-12-94

9406-076 (Closed) Gene Marking/Cancer/Pediatric Malignancies
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Heslop, Helen; Brenner, Malcolm, K.; and Krance, Robert; St. Jude Childrens Research Hospital, Memphis, Tennessee; *Use of Double Marking with Retroviral Vectors to Determine the Rate of Reconstitution of Untreated and Cytokine Expanded CD34(+) Selected Marrow Cells in Patients Undergoing Autologous Bone Marrow Transplantation.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 7-12-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9406-077 (Closed) Gene Therapy/Phase I/Cancer/Breast/Chemoprotection
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Intravenous

Deisseroth, Albert; Hortobagyi, Gabriel; Champlin, Richard; and Holmes, Frankie; MD Anderson Cancer Center, Houston, Texas; *Use of Safety-Modified Retroviruses to Introduce Chemotherapy Resistance Sequences into Normal Hematopoietic Cells for Chemoprotection During the Therapy of Breast Cancer: A Pilot Trial.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 7-12-94

9406-078 (Closed) Gene Therapy/Phase I/Monogenic Disease/Fanconi Anemia
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Fanconi Anemia Complementation Group C cDNA/Intravenous

Liu, Johnson, M. and Young, Neal S.; National Institutes of Health, Bethesda, Maryland; and Wagner, John E., University of Minnesota, Minneapolis, Minnesota; *Retroviral Mediated Gene Transfer of the Fanconi Anemia Complementation Group C Gene to Hematopoietic Progenitors of Group C Patients.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 2-12-95
Closed: 1997, follow-up continuing

9406-079 (Closed) Gene Therapy/Phase I/Cancer/Non-small Cell Lung Cancer/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral/Bronchoscope

Roth, Jack A.; MD Anderson Cancer Center, Houston, Texas; *Clinical Protocol for Modification of Tumor Suppressor Gene Expression and Induction of Apoptosis in Non-Small Cell Lung Cancer (NSCLC) with an Adenovirus Vector Expressing Wildtype p53 and Cisplatin.*

*RAC Recommends Approval: 6-10-94 and 9-11-95/NIH Approval: 9-21-95

9406-080 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Immunotherapy
In Vitro/Autologous Fibroblasts/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Sobol, Robert and Royston, Ivor; San Diego Regional Cancer Center; San Diego, California; *Injection of Glioblastoma Patients with Tumor Cells Genetically Modified to Secrete Interleukin-2 (IL-2): A Phase I Study.*

*RAC Recommends Approval: 6-10-94/NIH Approval: 7-12-94

9406-081 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Lymphoma/Breast/Head and Neck Cancer/Immunotherapy
In Vitro/Autologous Fibroblasts/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-12 cDNA/Neomycin Phosphotransferase cDNA/Intratumoral/Direct Injection

Lotze, Michael T; University of Pittsburgh, Pittsburgh, Pennsylvania; *IL-12 Gene Therapy Using Direct Injection of Tumor with Genetically Engineered Autologous Fibroblasts.*

*RAC Recommends Approval: 6-10-94/NIH Approval: 2-10-95

9408-082 (Closed) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Subcutaneous Injection

Simons, Jonathan; Johns Hopkins Oncology Center, Baltimore, Maryland; *Phase I/II Study of Autologous Human GM-CSF Gene Transduced Prostate Cancer Vaccines in Patients with Metastatic Prostate Carcinoma.*
NIH/ORDA Approval: 8-3-94 (Accelerated Review)

Study closed, long-term follow-up continues: 7-16-01

9409-083 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Zeitlin, Pamela L.; Johns Hopkins Childrens Center, Baltimore, Maryland and Flotte, Terence R., University of Florida, Gainesville, Florida; *A Phase I Study of an Adeno-associated Virus-CFTR Gene Vector in Adult CF Patients with Mild Lung Disease.* Sponsor: Targeted Genetics Corporation

*RAC Recommends Approval: 9-12-94/NIH Approval: 11-15-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9409-084 (Open) Gene Therapy/Phase I/Cancer/Breast/Antisense
In Vivo/Autologous Tumor Cells/Retrovirus/c-fos Antisense RNA/c-myc Antisense/Intrapleural/Intraperitoneal

Holt, Jeffrey, and Arteaga, Carlos B.; Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; *Gene Therapy for the Treatment of Metastatic Breast Cancer by In Vivo Infection with Breast-Targeted Retroviral Vectors Expressing Antisense c-fos or Antisense c-myc RNA.*

*RAC Recommends Approval: 9-12-94/NIH Approval: 1-4-95

9409-085 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)/Multiple Dose

Crystal, Ronald G.; New York Hospital-Cornell Medical Center, New York, New York; *Evaluation of Repeat Administration of a Replication Deficient, Recombinant Adenovirus Containing the Normal Cystic Fibrosis Transmembrane Conductance Regulator cDNA to the Airways of Individuals with Cystic Fibrosis.*

*RAC Recommends Approval: 9-12-94/NIH Approval: 11-30-94

9409-086 (Closed) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Avectin™/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Lyerly, H. Kim; Duke University Medical Center, Durham, North Carolina; *A Pilot Study of Autologous Human Interleukin-2 Gene Modified Tumor Cells in Patients with Refractory or Recurrent Metastatic Breast Cancer.*

*RAC Recommends Approval: 9-12-94/NIH Approval: 10-25-94

9409-087 (Open) Gene Therapy/Phase I/Monogenic Disease/Hunter Syndrome
In Vitro/Autologous Peripheral Blood Cells/Retrovirus/Iduronate-2-Sulfatase cDNA/Intravenous

Whitley, Chester B.; University of Minnesota, Minneapolis, Minnesota; *Retroviral-Mediated Transfer of the Iduronate-2-Sulfatase Gene into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II).*

*RAC Recommends Approval: 9-13-94/NIH Approval: 8-20-95

9409-088 (Closed) Gene Therapy/Phase I/Other/Peripheral Artery Disease
In Vivo/Vascular Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor cDNA/Intraarterial/Angioplasty Catheter/Hydrogel Coated Balloon

Isner, Jeffrey M. and Walsh, Kenneth; St. Elizabeth's Medical Center, Tufts University, Boston, Massachusetts; *Arterial Gene Transfer for Therapeutic Angiogenesis in Patients with Peripheral Artery Disease.*

*RAC Recommends Approval: 9-13-94/NIH Approval: 11-15-94
Follow-up has been completed: 11-29-01

9409-089 (Closed) Gene Therapy/Phase I/Cancer/Central Nervous System/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Stereotactic Injection

Eck, Stephen L. and Alavi, Jane B.; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Treatment of Advanced CNS Malignancy with the Recombinant Adenovirus H5.020RSVTK: A Phase I Trial.*

*RAC Recommends Approval: 9-13-94/NIH Approval: 2-2-96

9409-090 (Closed) Gene Therapy/Phase I/Cancer/n/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intrapleural

Albelda, Steven M.; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Treatment of Advanced Mesothelioma with the Recombinant Adenovirus H5.010RSVTK: A Phase I Trial.*

*RAC Recommends Approval: 9-13-94/NIH Approval: 1-4-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9409-091 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Respiratory Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Respiratory Epithelial Cells/Bronchoscope

Dorkin, Henry L.; New England Medical Center, Tufts University, Boston, Massachusetts; and Lapey, Allen; Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; *Adenovirus Mediated Gene Transfer for Cystic Fibrosis: Safety of Single Administration in the Lung (lobar instillation).* Sponsor: Genzyme Corporation

NIH/ORDA Approval: 10-5-94 (Accelerated Review)
Protocol ended in December 1997

9411-092 (Closed) Gene Marking/Cancer/Lymphoma/Breast
In Vitro/CD34+ Autologous Bone Marrow Cells/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Douer, Dan; University of Southern California; Kenneth Norris Comprehensive Cancer Center and Hospital, Los Angeles, California; *High Dose Chemotherapy and Autologous Bone Marrow plus Peripheral Blood Stem Cell Transplantation for Patients with Lymphoma or Metastatic Breast Cancer: Use of Marker Genes to Investigate the Biology of Hematopoietic Reconstitution in Adults.*

NIH/ORDA Approval: 11-18-94 (Accelerated Review)

Notification that trial has been closed: 6-13-01

9411-093 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Subcutaneous Injection

Dranoff, Glen; Dana Farber Cancer Institute, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Irradiated Melanoma Cells Engineered to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.*

NIH/ORDA Approval: 11-23-94 (Accelerated Review)

Study closed, long-term follow-up continues: 7-16-01

9412-094 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Respiratory Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Respiratory Epithelial Cells/Aerosol Administration

Dorkin, Henry L.; New England Medical Center, Tufts University, Boston, Massachusetts; and Lapey, Allen; Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; *Adenovirus Mediated Gene Transfer for Cystic Fibrosis: Safety of a Single Administration in the Lung (aerosol administration).* Sponsor: Genzyme Corporation

*RAC Recommends Approval: 12-1-94/NIH Approval: 7-24-95
Protocol ended in December 1997

9412-095 (Closed) Gene Therapy/Phase I/Solid Tumors/Lymphoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1102/Cytokine/Interleukin-2 cDNA/Intratumoral/Direct Injection

Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; and Rinehart, John; Scott and White Clinic; Temple Texas. *Phase I Trial of Interleukin-2 Plasmid DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Solid Malignant Tumors or Lymphomas by Direct Gene Transfer.* Sponsor: Vical, Incorporated

*RAC Recommends Approval: 12-1-94/NIH Approval: 3-2-95

9412-096 (Closed) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral/Bronchoscope

Clayman, Gary; MD Anderson Cancer Center, Houston, Texas; *Clinical Protocol for Modification of Tumor Suppressor Gene Expression in Head and Neck Squamous Cell Carcinoma (HNSCC) with an Adenovirus Vector Expressing Wild-type p53.*

*RAC Recommends Approval: 12-2-94 and 9-11-95/NIH Approval: 9-21-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9412-097 (Open) Gene Therapy/Phase I/Cancer/Colon/Hepatic Metastases/Tumor Suppressor Gene In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intrahepatic/Hepatic Artery/Bolus Infusion

Venook, Alan and Warren, Robert; Moffitt-Long Hospital of the University of California, San Francisco Medical Center; *Gene Therapy of Primary and Metastatic Malignant Tumors of the Liver Using ACN53 Via Hepatic Artery Infusion: A Phase I Study.* Sponsor: Schering Plough Corporation (formerly Canji)

RAC Recommends Approval Contingent Upon Meeting Stipulations: 12-2-94

9412-098 (Open) Gene Therapy/Phase I/Cancer/Central Nervous System Malignancies/Pro-Drug In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intra- tumoral/Stereotactic Injection

Grossman, Robert and Woo, Savio; The Methodist Hospital, Houston, Texas; *Phase I Study of Adenoviral Vector Delivery of the HSV-TK Gene and the Intravenous Administration of Ganciclovir in Adults with Malignant Tumors of the Central Nervous System.*

*RAC Recommends Approval: 12-2-94/NIH Approval: 2-2-96

9502-099 (Open) Gene Therapy/Phase I/Cancer/Astrocytoma/Pro-Drug In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Stereotactic Injection

Fetell, Michael; Columbia Presbyterian Medical Center, New York, New York; Warnick, Ronald; University of Cincinnati, Cincinnati, OH; Yung, W.K. Alfred; M.D. Anderson Cancer Center, Houston, Texas; Maria, Bernard L.; University of Florida, Gainesville, Florida; Shaffrey, Mark; University of Virginia Health Sciences Center, Charlottesville, Virginia; Ram, Zvi; Chaim Sheba Medical Center, Tel Aviv University Sackler School of Medicine, Tel Hashomer, Israel; Prados, Michael; University of California, San Francisco, California; and Grossman, Stuart; Johns Hopkins University Hospital Oncology Center; Baltimore, Maryland; *Stereotactic Injection of Herpes Simplex Thymidine Kinase Vector Producer Cells (PA317/G1TkSvNa.7) and Intravenous Ganciclovir for the Treatment of Recurrent Malignant Glioma.* Sponsor: Genetic Therapy, Inc./Novartis

NIH/ORDA Approval: 2-10-95 (Accelerated Review)

9503-100 (Closed) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraperitoneal/Catheter

Link, Charles; Human Gene Therapy Research Institute; and Moorman, Donald; Iowa Methodist Medical Center, Des Moines, Iowa; *A Phase I Trial of In Vivo Gene Therapy with Herpes Simplex Thymidine Kinase/Ganciclovir System for the Treatment of Refractory or Recurrent Ovarian Cancer.*
*RAC Recommends Approval: 3-6-95/NIH Approval: 7-27-95

9503-101 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-7 cDNA/Hygromycin Phosphotransferase/Herpes Simplex Virus Thymidine Kinase cDNA/Subcutaneous Injection

Economou, James; Glaspy, John; and McBride, William; University of California, Los Angeles, California; *A Phase I Testing of Genetically Engineered Interleukin-7 Melanoma Vaccines.*

*RAC Recommends Approval: 3-6-95/NIH Approval: 8-20-95
Closed: 3-97

9503-102 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy In Vitro/HLA-Matched Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-2 cDNA/Gamma Interferon cDNA/Subcutaneous Injection

Gansbacher, Bernd; Memorial Sloan Kettering Cancer Center, New York, New York; *Phase I/II Study of Immunization with MHC Class I Matched Allogeneic Human Prostatic Carcinoma Cells Engineered to Secrete Interleukin-2 and Interferon-γ.*

RAC Recommends Approval Contingent Upon Meeting Stipulations: 3-6-95

9503-103 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense In Vitro/Antisense TAR/Transdominant Rev/Intravenous

Tavel, Jorge; National Institutes of Health, Bethesda, Maryland; *Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins.*

*RAC Recommends Approval: 3-7-95/NIH Approval: 4-1-95
Closed to new enrollment. Individuals will be followed, long-term, in a new protocol (that does not involve administration of recombinant DNA): 1-17-02

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9503-104 (Open) Gene Therapy/Phase I/Monogenic Disease/Chronic Granulomatous Disease
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/p47phox/Intravenous

Malech, Harry; National Institutes of Health, Bethesda, Maryland; *Gene Therapy Approach for Chronic Granulomatous Disease.*

*RAC Recommends Approval: 3-7-95/NIH Approval: 4-15-95

9503-105 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Parenti, David; George Washington University Medical Center, Washington, D.C.; Haubrich, Richard; University of California San Diego Treatment Center, San Diego, California; Frame, Peter; University of Cincinnati AIDS Treatment Center, Cincinnati, Ohio; Powderly, William; Washington University AIDS Clinical Trials Unit; St. Louis, Missouri; and Loveless, Mark; Oregon Health Sciences University, Portland, Oregon; *A Repeat Dose Safety and Efficacy Study of HIV-IT(V) in HIV-1 Infected Subjects with Greater Than or Equal to 100 CD4+ T Cells and No AIDS Defining Symptoms.*

NIH/ORDA Approval: 3-11-95 (Accelerated Review)

Notification that trial has been completed, IND is inactive: 5-22-00

9506-106 (Open) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/Autologous G-CSF and ATA-C Mobilized Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Verfaillie, Catherine; University of Minnesota, Minneapolis, Minnesota; *Autologous Marrow Transplantation for Chronic Myelogenous Leukemia Using Stem Cells Obtained After In Vivo Chemotherapy Cytokine Priming.*

NIH/ORDA Approval: 5-5-95

9506-107 (Open) Gene Therapy/Phase I/Cancer/Multiple Myeloma/Pro-Drug
In Vitro/Allogeneic T Lymphocytes/Retrovirus/Herpes Simplex Thymidine Kinase/Ganciclovir/Intravenous

Munshi, Nikhil C. and Barlogie, Bart; University of Arkansas for Medical Sciences, Little Rock, Arkansas; *Thymidine Kinase (TK) Transduced Donor Leukocyte Infusions as a Treatment for Patients with Relapsed or Persistent Multiple Myeloma after T-cell Depleted Allogeneic Bone Marrow Transplant.*
Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 6-9-95/NIH Approval: 7-27-95

9506-108 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Subcutaneous Injection

Fox, Bernard A. and Urba, Walter J.; Earle A. Chiles Research Institute, Providence Medical Center, Portland, Oregon; *Adoptive Cellular Therapy of Cancer Combining Direct HA-B7/β-2 Microglobulin Gene Transfer with Autologous Tumor Vaccination for the Generation of Vaccine-Primed Anti-CD3 Activated Lymphocytes.*

*RAC Recommends Approval: 6-9-95/NIH Approval: 9-30-95

9506-109 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Immunotherapy
In Vitro/Anti-CD3 Stimulated Autologous Peripheral Blood Lymphocytes/Retrovirus/Antibody/MOv-gamma (Reactive with Folate Binding Protein)/Intravenous/Intraperitoneal

Hwu, Patrick; National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Advanced Epithelial Ovarian Cancer using Anti-CD3 Stimulated Peripheral Blood Lymphocytes Transduced with a Gene Encoding a Chimeric T-cell Receptor Reactive with Folate Binding Protein.*

RAC Recommends Approval Contingent Upon Meeting Stipulations: 6-9-95

9506-110 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/DDAB-DOPE/Cytokine/Interleukin-2 cDNA/Intradermal Injection

Berchuck, Andres and Lyerly, H. Kim; Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Autologous Human Interleukin-2 (IL-2) Gene Modified Tumor Cells in Patients with Refractory Metastatic Ovarian Cancer.*

*RAC Recommends Approval: 6-10-95/NIH Approval: 9-30-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9506-111 (Closed) Gene Therapy/Phase I/Monogenic Disease/Purine Nucleoside Phosphorylase Deficiency
In Vitro/Autologous Peripheral Blood Lymphocytes/Retrovirus/Purine Nucleoside Phosphorylase cDNA/Intravenous

McIvor, R. Scott; Institute of Human Genetics, University of Minnesota, Minneapolis, Minnesota; *Gene Therapy for Purine Nucleoside Phosphorylase Deficiency.*

*RAC Recommends Approval: 6-9-95/NIH Approval: 7-27-95
Closed: 9-24-00 No individuals enrolled, IND not submitted

9506-112 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Single Chain Antibody Gene/In Vitro/CD4+ Autologous Peripheral Blood Lymphocytes/Retrovirus/sFv105 Anti-HIV-1 Envelope Protein(gp160)Gene/Intravenous

Marasco, Wayne A.; Dana Farber Cancer Institute, Boston, Massachusetts; *Intracellular Antibodies Against HIV-1 Envelope Protein for AIDS Gene Therapy.*
*RAC Recommends Approval: 6-9-95/NIH Approval: 7-27-95

9504-113 (Closed) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus-1/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Conant, Marcus, Conant Medical Group; Lang, William, ViRx, Inc.; and Merritt, James, Viagene, Inc., San Francisco, California; *A Randomized, Double Blinded, Phase I/II Dosing Study to Evaluate the Safety and Optimal CTL Inducing Dose of HIV-IT(V) in Pre-Selected HIV-1 Infected Subjects.*

*RAC Recommends Approval: NA/NIH Approval: NA (Non-NIH funded institution)
FDA Approval: 5-6-94

9507-114 (Open) Gene Therapy/Phase I-II/Monogenic Disease/Cystic Fibrosis
In Vivo/Maxillary Sinus Epithelial Cells/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Maxillary Sinus Administration

Gardner, Phyllis; Stanford University School of Medicine, Stanford, California; *A Phase I/II Study of tg-CF for the Treatment of Chronic Sinusitis in Patients with Cystic Fibrosis.* Sponsor: Targeted Genetics Corporation

Sole FDA Review Recommended by NIH/ORDA: 7-11-95

9508-115 (Closed) Gene Therapy/Phase II/Cancer/Metastatic Malignancies(Breast Adenocarcinoma, Renal Cell Carcinoma, Melanoma, Colorectal Adenocarcinoma, non-Hodgkin's Lymphoma)/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Chang, Alfred E.; University of Michigan Medical Center, Ann Arbor, Michigan; Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; Vogelzang, Nicholas; University of Chicago Medical Center, Chicago, Illinois; Levy, Ronald; Stanford University Medical Center, Palo Alto, California; Redman, Bruce; Wayne State University School of Medicine; Detroit, Michigan; Figlin, Robert; University of California Medical Center, Los Angeles, California; Rubin, Joseph; Mayo Foundation for Medical Evaluation and Research, Rochester, Minnesota; Rinehart, John J.; Scott and White Hospital, Texas A & M University, Temple Texas; Doroshow, James H.; City of Hope National Medical Center, Duarte, California; Klasa, Richard; British Columbia Cancer Agency, Vancouver, British Columbia; Sobol, Robert; Sidney Kimmel Cancer Center, San Diego, California; *Phase II Study of Immunotherapy of Metastatic Cancer by Direct Gene Transfer.* Sponsor: Vical, Incorporated

Sole FDA Review Recommended by NIH/ORDA: 8-2-95

9508-116 (Open) Gene Therapy/Phase I/Cancer/Glioma/Immunotherapy
In Vitro/Autologous Tumor (Glioma) Cells/Non-Irradiated/Retrovirus/Cytokine/Interleukin-4 cDNA/Subcutaneous Injection

Pollack, Ian; Okada, Hideho; and Lotze, Michael T.; University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; *Gene Therapy of Malignant Gliomas: A Phase I Study of IL-4 Gene -Modified Autologous Tumor to Elicit an Immune Response.*

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-117 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition
In Vitro/Autologous CD34+ Peripheral Blood Cells/Retrovirus/Hammerhead Ribozyme/Intravenous

Mitsuyasu, Ronald; University of California Los Angeles, California; *A Phase I Trial of Autologous CD34+ Hematopoietic Progenitor Cells Transduced with an Anti-HIV-1 Ribozyme.*

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9508-118 (Open) Gene Therapy/Phase I/Other/Restenosis
In Vivo/Vascular Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor cDNA/Intraarterial/Angioplasty Catheter/Hydrogel Coated Balloon

Losordo, Douglas W.; St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts; *Accelerated Re-endothelialization and Reduced Neointimal Thickening Following Catheter Transfer of phVEGF165.*

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-119 (Open) Gene Therapy/Phase I/Human Immunodeficiency Virus-1
In Vitro/CD8+ Allogeneic Cytotoxic T Lymphocytes/CD8+ Syngeneic Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase/Herpes Simplex Virus Thymidine Kinase cDNA/Retrovirus/Intravenous

Riddell, Stanley R.; Fred Hutchinson Cancer Research Center, Seattle, Washington; *Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy using Autologous Unmodified and Genetically Modified CD8+ HIV-Specific T Cells in HIV Seropositive Individuals.* Sponsor: Targeted Genetics Corporation

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-120 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Used to Derive Tumor Infiltrating Lymphocytes/HLA-B7 cDNA/Intravenous

Chang, Alfred E. and Nabel, Gary J.; University of Michigan Medical Center, Ann Arbor, Michigan; *Phase I Study of Tumor-Infiltrating Lymphocytes Derived from In Vivo HLA-B7 Gene Modified Tumors in the Adoptive Immunotherapy of Melanoma.*

Sole FDA Review Recommended by NIH/ORDA: 8-14-95

9508-121 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vivo/Autologous Tumor Cells/HLA B7 cDNA/Intratumoral/Concurrent Interleukin-2 Therapy

Figlin, Robert A.; University of California Los Angeles Medical Center, Los Angeles, California; *Phase I Study of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Renal Cell Carcinoma by Direct Gene Transfer with Concurrent Low Dose Bolus IL-2 Protein Therapy.* Sponsor: Vical, Incorporated

Sole FDA Review Recommended by NIH/ORDA: 8-14-95

9508-122 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies (type of cancer not specified)/Immunotherapy
In Vivo/Autologous Muscle Cells/Canarypox Virus/Carcinoembryonic Antigen cDNA/Intramuscular Injection

Hawkins, Michael J. and Marshall, John L.; Georgetown University Medical Center, Washington, D.C.; *A Study of Recombinant ALVAC Virus that Expresses Carcinoembryonic Antigen in Patients with Advanced Cancers.*

Sole FDA Review Recommended by NIH/ORDA 8-14-95

9509-123 (Open) Gene Therapy/Phase I/Cancer/Prostate/Antisense
In Vivo/Autologous Tumor Cells/Retrovirus/Antisense c-myc RNA/Intraprostate Injection

Steiner, Mitchell S., Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; and Holt, Jeffrey T., Vanderbilt University School of Medicine, Nashville, Tennessee; *Gene Therapy for the Treatment of Advanced Prostate Cancer by In Vivo Transduction with Prostate-Targeted Retroviral Vectors Expressing Antisense c-myc RNA.*

*RAC Recommends Approval: 9-11-95/NIH Approval: 9-30-95

9509-124 (Open) Gene Therapy/Phase I/Cancer/Ovarian and Extraovarian/Anti-erbB-2 Single Chain Antibody Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Anti-erbB-2 (oncoprotein/extracellular domain) Single-chain Antibody Gene/Intraperitoneal Injection

Curiel, David T. and Alvarez, Ronald D.; University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Study of Recombinant Adenovirus Vector-Mediated Delivery of an Anti-erbB-2 Single Chain (sFv) Antibody Gene for Previously Treated Ovarian and Extraovarian Cancer Patients.*

RAC Recommends Approval Contingent Upon Meeting Stipulations: 9-11-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9509-125 (Closed) Gene Therapy/Phase I/Cancer/Colon Carcinoma (Hepatic Metastases)/Pro-Drug In Vivo/Autologous Tumor Cells/Adenovirus/E. coli Cytosine Deaminase cDNA/Intratumoral (Hepatic) Injection/Combined with Oral 5-Fluorocytosine

Crystal, Ronald, G.; Hershowitz, Edward; and Lieberman, Michael; New York Hospital-Cornell Medical Center, New York, New York; *A Phase I Study of Direct Administration of a Replication-Deficient Adenovirus Vector Containing the E. coli Cytosine Deaminase Gene to Metastatic Colon Carcinoma of the Liver in Association with the Oral Administration of the Pro-Drug 5-Fluorocytosine.*

*RAC Recommends Approval: 9-11-95/NIH Approval: 9-30-95
Notification that IND has been withdrawn: 2-2-00

9509-126 (Open) Gene Therapy/Phase I/Cancer/Prostate Adenocarcinoma/Immunotherapy In Vivo/Vaccination/Vaccinia Virus/Prostate Specific Antigen/Intradermal Injection

Chen, A.P.; National Naval Medical Center, Bethesda, Maryland; *A Phase I Study of Recombinant Vaccinia that Expresses Prostate Specific Antigen in Adult Patients with Adenocarcinoma of the Prostate.*

Sole FDA Review Recommended by NIH/ORDA: 9-22-95

9509-127 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis In Vivo/Nasal Epithelial Cells/Cationic Liposome Complex/DOPE/Cystic Fibrosis Transmembrane Conductance Regulator cDNA; Intranasal Administration

Welsh, Michael J. and Zabner, Joseph; Howard Hughes Medical Institute, University of Iowa College of Medicine, Iowa City, Iowa; *Cationic Lipid Mediated Gene Transfer of CFTR: Safety of a Single Administration to the Nasal Epithelia.* Sponsor: Genzyme Corporation

Sole FDA Review Recommended by NIH/ORDA: 9-26-95

9510-128 (Open) Gene Therapy/Phase I/Cancer/Gastrointestinal Tract, Breast, or Lung Adenocarcinoma (CEA-Expressing Malignancies)/Immunotherapy/In Vivo/Vaccination/Vaccinia Virus/Carcinoembryonic Antigen/Intradermal Injection in Combination with Subcutaneous Peptide Challenge

Cole, David J.; Medical University of South Carolina, Charleston, South Carolina; *Phase I Study of Recombinant CEA Vaccinia Virus Vaccine with Post Vaccination CEA Peptide Challenge.*

Sole FDA Review Recommended by NIH/ORDA: 10-16-95

9510-129 (Open) Gene Marking/Cancer/EBV-Positive Hodgkin Disease In Vitro/EBV-Specific Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Roskrow, Marie; Hudson, Melissa; Rooney, Cliona; Heslop, Helen; and Brenner, Malcolm; St. Jude Children's Research Hospital, Memphis, Tennessee; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes as Therapy for Patients Receiving a Bone Marrow Transplant for Relapsed EBV-Positive Hodgkin Disease.*

Sole FDA Review Recommended by NIH/ORDA: 10-17-95

9510-130 (Open) Gene Marking/Cancer/EBV-Positive Hodgkin Disease In Vitro/EBV-Specific Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Administration

Roskrow, Marie; Hudson, Melissa; Rooney, Cliona; Heslop, Helen; and Brenner, Malcolm; St. Jude Children's Research Hospital, Memphis, Tennessee; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin Disease.*

Sole FDA Review Recommended by NIH/ORDA: 10-17-95

9510-131 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus In Vitro/Autologous CD8+ T Cells/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous

Connick, Elizabeth; University of Colorado Health Sciences Center, Denver, Colorado; and Deeks, Steven G.; University of California, San Francisco General Hospital, San Francisco, California; *A Randomized, Controlled, Phase II Study of the Activity and Safety of Autologous CD4-Zeta Gene-Modified T Cells in HIV-Infected Patients.* Sponsor: Cell Genesys, Inc.

Sole FDA Review Recommended by NIH/ORDA: 10-17-95
Closed 8-6-97 (No longer enrolling patients)

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9510-132 (Open) Gene Therapy/Phase I/Cancer/Locally Advanced or Metastatic Prostate/Immunotherapy In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Cytokine/Interleukin-2 cDNA/Intradermal Injection

Paulson, David; and Lyerly, H. Kim; Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Autologous Human Interleukin-2 (IL-2) Gene Modified Tumor Cells in Patients with locally Advanced or Metastatic Prostate Cancer.*

Sole FDA Review Recommended by NIH/ORDA: 10-19-95

9511-133 (Closed) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy In Vitro/Autologous Tumor Cells (Non-irradiated)/Type 5 Adenovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Brenner, Malcolm K.; Dilloo, Dagmar; and Bowman, Laura; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9511-134 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition In Vitro/Autologous CD4+ T Cells/Retrovirus/Neomycin Phosphotransferase Gene/PolyTAR Decoy Gene/RRE-polyTAR Decoy Gene

Greenberg, Philip D.; Fred Hutchinson Cancer Research Center, University of Washington Medical Center, Seattle, Washington; *Phase I Study to Evaluate the Safety and In Vivo Persistence of Adoptively Transferred Autologous CD4+ T Cells Genetically Modified to Resist HIV Replication.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

Trial is closed to new accrual; follow-up will continue: 03-19-01

9511-135 (Open) Gene Therapy/Phase I/Cancer/Ovarian and Extraovarian Cancer/Single Chain Antibody In Vivo/Autologous Tumor Cells/Adenovirus/Herpes Simplex Thymidine Kinase Gene/Intraperitoneal Injection/Combined with Intravenous Ganciclovir Administration

Alvarez, Ronald D. and Curiel, David T.; University of Alabama Comprehensive Cancer Center, Birmingham, Alabama; *A Phase I Study of Recombinant Adenovirus Vector-Mediated Intraperitoneal Delivery of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Gene and Intravenous Ganciclovir for Previously Treated Ovarian and Extraovarian Cancer Patients.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9511-136 (Open) Gene Therapy/Phase I/Cancer/Metastatic Melanoma/Immunotherapy In Vitro/Autologous CD8+ Tyrosinase-Specific TCells/Retrovirus/Hygromycin Phosphotransferase/Intravenous Administration

Yee, Cassian and Greenberg, Philip D.; Fred Hutchinson Cancer Research Center, University of Washington Medical Center, Seattle, Washington; *Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy Using Autologous Unmodified and Genetically Modified CD8+ Tyrosinase-Specific T Cells in Patients with Metastatic Melanoma.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9512-137 (Open) Gene Therapy/Phase I/Cancer/Ovarian,Breast/Oncogene Regulation/HER-2/*neu* In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intraperitoneal, Intrapleural Administration

Hortobagyi, Gabriel N.; Lopez-Berstein, Gabriel; and Hung, Mien-Chien; MD Anderson Cancer Center, Houston, Texas; Kilbourn, Robert, Rush-Presbyterian/St. Luke's Medical Center, Chicago, Illinois; Weiden, Paul; Virginia Mason Medical Center, Seattle, Washington; *Phase I Study of E1A Gene Therapy for Patients with Metastatic Breast or Ovarian Cancer that Overexpresses Her-2/neu.* Sponsor: Targeted Genetics Corporation

*RAC Recommends Approval: 12-4-95/NIH Approval: 2-2-96

9512-138 (Open) Gene Therapy/Phase I/Cancer/Malignant Glioma/Antisense In Vitro/Autologous Tumor Cells/Lethally Irradiated/Plasmid DNA--Electroporation/TGF-β2/Subcutaneous Injection

Black, Keith L.; and Fakhrai, Habib; University of California, Los Angeles, School of Medicine, Los Angeles, California; *A Phase I Study of the Safety of Injecting Malignant Glioma Patients with Irradiated TGF-β2 Antisense Gene Modified Autologous Tumor Cells.*

*RAC Recommends Approval: 12-4-95/NIH Approval: 4-2-96

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9512-139 (Open) Gene Therapy/Phase I/Monogenic Disease/Partial Ornithine Transcarbamylase (OTC) Deficiency In Vivo/Autologous Peripheral Blood Cells/Adenovirus/Type 5 (E2a Temperature-Sensitive Mutant)/Ornithine Transcarbamylase cDNA/Intravenous

Batshaw, Mark; Institute for Human Gene Therapy, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *A Phase I Study of Adenoviral Vector Mediated Gene Transfer to Liver in Adults with Partial Ornithine Transcarbamylase Deficiency.*

RAC Recommends Approval Contingent Upon Meeting Stipulations: 12-4-95

9512-140 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/ In Vivo/Adenovirus/Type 2/MART-1 Melanoma Antigen/Subcutaneous Injection/Immunization

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the MART-1 Melanoma Antigen.*

Sole FDA Review Recommended by NIH/ORDA: 12-1-95

9512-141 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition In Vitro/Autologous CD4+ Peripheral Blood Lymphocytes/Retrovirus/Anti-Rev SFv/Intravenous

Pomerantz, Roger J; Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania; *Intracellular Immunization Against HIV-1 Infection Using an Anti-Rev Single Chain Variable Fragment (SFv).*

Sole FDA Review Recommended by NIH/ORDA: 12-13-95

9512-142 (Open) Gene Therapy/Phase I/Gene Therapy/Cancer/Head and Neck Squamous Cell Carcinoma/Immunotherapy In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Gluckman, Jack L.; University of Cincinnati Medical Center, Cincinnati, Ohio; *Allovectin-7 in the Treatment of Squamous Cell Carcinoma of the Head and Neck.*

Sole FDA Review Recommended by NIH/ORDA: 12-15-95

9601-143 (Closed) Gene Therapy/Phase I/Cancer/Breast/Chemoprotection In Vitro/Autologous CD34+ Peripheral Blood Lymphocytes//Retrovirus/Multi-Drug Resistance-1 cDNA/Neomycin Phosphotransferase cDNA/Intravenous

Cowan, Kenneth H.; National Institutes of Health, Bethesda, Maryland; *Antimetabolite Induction, High-Dose Alkylating Agent Consolidation, and Retroviral Transduction of the MDR1 Gene Into Peripheral Blood Progenitor Cells Followed by Intensification Therapy with Sequential Paclitaxel and Doxorubicin for Stage 4 Breast Cancer.*

Sole FDA Review Recommended by NIH/ORDA: 1-26-96
Closed: 6-14-00

9601-144 (Open) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Intra-prostatic Tumor Injection

Scardino, Peter T.; Thompson, TImothy C.; and Woo, Savio L.C.; Baylor College of Medicine, Houston, Texas; *Phase I Study of Adenoviral Vector Delivery of the HSV-tk Gene and the Intravenous Administration of Ganciclovir in Men with Local Recurrence of Prostate Cancer after Radiation Therapy.*

Sole FDA Review Recommended by NIH/ORDA: 1-29-96

9601-145 (Closed) Gene Therapy/Phase I/Cancer/Bladder/Tumor Suppressor Gene In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Retinoblastoma cDNA/Intravesical Catheter Administration

Small, Eric J. and Carroll, Peter R.; University of California, San Francisco, California; *Gene Therapy of Bladder Cancer Using Recombinant Adenovirus Containing the Retinoblastoma Gene (ACNRB): A Phase IA Study.* Sponsor: Schering Plough Corporation (formerly Canji)

Sole FDA Review Recommended by NIH/ORDA: 1-30-96
Canceled: 4-4-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9602-146 (Open) Gene Therapy/Phase I/Cancer/Hematologic Malignancies Following Allogeneic Bone Marrow Transplant/Pro-Drug/Elimination of Graft Versus Host Disease
In Vitro/Allogeneic Peripheral Blood Lymphocytes/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intravenous

Link, Charles J.; Human Gene Therapy Research Institute, Des Moines, Iowa; Burt, Richard K. and Traynor, Ann; Northwestern University School of Medicine, Chicago, Illinois; *Adoptive Immunotherapy for Leukemia: Donor Lymphocytes Transduced with the Herpes Simplex Thymidine Kinase Gene for Remission Induction.*

Sole FDA Review Recommended by NIH/ORDA: 2-8-96

9602-147 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/RRE Decoy Gene, and Retrovirus/Neomycin Phosphotransferase Gene/Intravenous

Kohn, Donald B.; Childrens Hospital Los Angeles, Los Angeles, California; *Transduction of CD34+ Cells from the Bone Marrow of HIV-1 Infected Children: Comparative Marking by an RRE Decoy and a Neutral Gene.*

Sole FDA Review Recommended by NIH/ORDA: 2-8-96

9602-148 (Open) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell Carcinoma/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

O'Malley, Bert W.; Johns Hopkins University, Baltimore, Maryland; *Phase I Study of Adenoviral Vector Delivery of the HSV-tk Gene and the Intravenous Administration of Ganciclovir in Adults with Recurrent or Persistent Head and Neck Cancer.*

Sole FDA Review Recommended by NIH/ORDA: 2-13-96

9603-149 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Retrovirus/BRCA-1 Gene/Intraperitoneal Administration (Ultrasound Guided)

Holt, Jeffrey T.; Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; *Ovarian Cancer Gene Therapy with BRCA-1.*

Sole FDA Review Recommended by NIH/ORDA: 3-6-96

9603-150 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy In Vivo/Autologous Tumor Cells/HLA B7 cDNA/Intratumoral/Concurrent Interleukin-2 Therapy

Hersh, Evan M.; Arizona Cancer Center, Tucson, Arizona; and Sondak, Vernon K.; University of Michigan Medical Center, Ann Arbor, Michigan; *Evaluation of Intratumoral Gene Therapy with HLA-B7/DMRIE/DOPE plus Subcutaneous Low Dose Il-2.*

Sole FDA Review Recommended by NIH/ORDA; 3-26-96

Closed: 3-11-97. Protocol Never Initiated

9604-151 (Closed) Gene Therapy/Phase I/ Cancer/Melanoma/Immunotherapy In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 2/GP100 Melanoma Antigen/Subcutaneous or Intramuscular Injection/Concurrent Interleukin-2 Therapy

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the GP100 Melanoma Antigen.*

Sole FDA Review Recommended by NIH/ORDA: 4-19-96

9604-152 (Open) Gene Therapy/Phase I/Inherited Genetic Disorder/Monogenic Disease/X-Linked Severe Combined Immune Deficiency/Correction In Vitro/CD34+ Autologous Umbilical Cord Blood or Bone Marrow/Retrovirus/cDNA for Common γ Chain of Multiple Cytokine Receptors/Intravenous

Weinberg, Kenneth I.; Childrens Hospital Los Angeles (CHLA) ; Los Angeles, California; *Gene Therapy for X-linked Severe Combined Immune Deficiency using Retroviral Mediated Transduction of the γc cDNA into CD34+ Cells.*

Sole FDA Review Recommended by NIH/ORDA: 4-24-96

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9604-153 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Hammerhead Ribozyme/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Tat and Rev Hammerhead Ribozyme/Intravenous

Kohn, Donald B.; Childrens Hospital of Los Angeles (CHLA), Los Angeles, California; and Zaia, John A.; City of Hope National Medical Center, Duarte, California; *Transduction of CD34+ Autologous Peripheral Blood Progenitor Cells from HIV-1 Infected Persons: a Phase I Study of Comparative Marking Using a Ribozyme Gene and a Neutral Gene.*

Sole FDA Review Recommended by NIH/ORDA: 4-24-96

9605-154 (Closed) Gene Therapy/Phase I/Cancer/Brain Tumors/Pro-Drug/In Vivo/Autologous Tumor Cells/psiCRIP-MFG-S-TK1-67 Cells/Retrovirus/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Harsh IV, Griffith R.; Chiocca, E. Antonio; and Hochberg, Fred H.; Harvard Medical School, Boston, Massachusetts; *Phase I Study of Retroviral-Mediated Incorporation of the HSV Thymidine Kinase Gene and Ganciclovir in Malignant Gliomas.*

Sole FDA Review Recommended by NIH/ORDA: 5-1-96

9605-155 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Cationic Liposome Complex/B7(CD80) cDNA/Retrovirus/Herpes Simplex Thymidine Kinase/Ganciclovir/Intraperitoneal

Freeman, Scott M.; and Robinson III, William R.; Tulane University School of Medicine, New Orleans, Louisiana; *Tumor Vaccination With HER-2/Neu Using a B7 Expressing Tumor Cell Line Prior To Treatment With HSV-TK Gene-Modified Cells.*

Sole FDA Review Recommended by NIH/ORDA: 5-2-96

9608-156 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/B7(CD80) cDNA/Subcutaneous Injection

Urba, Walter J.; Providence Portland Medical Center, Portland, Oregon; *Phase I Trial Using a CD80-Modified Allogeneic Breast Cancer Line to Vaccinate HLA-A2-Positive Women with Breast Cancer .*

Sole FDA Review Recommended by NIH/ORDA: 8-6-96

9608-157 (Closed) Gene Therapy/Phase III of #9303-037/Cancer/Glioblastoma/Pro-Drug/In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Maria, Bernard; University of Florida, Gainsville, Florida; Gutheil, John; Sharp Healthcare, Sidney Kimmel Cancer Center, San Diego, California; Bucholz, Richard; St. Louis University, St. Louis, Missouri; Olson, Jeffrey; Emory School of Medicine, Winship Cancer Center, Atlanta, Georgia; Lillehei, Kevin; University of Colorado, Denver, Colorado; Van Gilder, John; University of Iowa College of Medicine, Iowa City, Iowa; Nemunaitis, John; Texas Oncology P.A., Baylor University Medical Center, Dallas, Texas; Origitano, Thomas; Loyola University Medical Center, Maywood, Illinois; Warnick, Ronald; University of Cincinnati Medical Center, The Christ Hospital, Good Samaritan Hospital, Jewish Hospital of Cincinnati, Veterans Affairs Medical Center, Cincinnati, Ohio; Weber, Friederich Dr. med.; Heinrich Heine Universtat, Dusseldorf, Germany; Rainov, Nikolai, PD Dr. med.; Martin Luther Universtat, Halle, Germany; Cloughesy, Timothy; UCLA Department of Neurology, Reed Neurological Research Center, Boywer Oncology Clinic, Los Angeles, California; Markert, James; University of Alabama at Birmingham, Birmingham, Alabama; Matti Vapalahti, Kuopio Universiy Hopsital, Kuopio, Finland; Yasuhiro Yonekawa, University Hospital, Zurich, Switzerland; Nanno Harrie Mulder, Academic Hospital Groningen, Groningen, The Netherlands; Susanne Osante, Academic Hospital Leiden, Leiden, The Netherlands; Fetell, Michael; Columbia-Presbyterian Medical Center Neurological Institute, New York, New York; Schramm, Johannes; Prof. Dr. med., Univ. Klinikum Neurochirurgische Klinik, Bonn, Germany; Westphal, Manfred, PD Dr. med.; Klinikum Eppendorf Neurochirurgie/Univ. Martinstr. 52, Hamburg, Germany; Tonn, Jorg-Christian, PD Dr. med.; u. Poliklinik/Univ. Kliniken, Wurzberg, Germany; Moumdjian, Robert, Dr.; Hospital Notre-Dame, Montreal, Quebec, Canada; Shaffrey, Mark; University of Virginia, Charlottesville, Virginia; Asher, Anthony; Presbyterian Hospital, Cancer Center, Charlotte, North Carolina; Epstein, Mel; Brown University, Providence, Rhode Island; Schmidt-Schackert, Frau.Prof. Dr. med.; Gabriele, Univ.-Klin. Kar-G. Carus, Klinik f. Neurochirurgie, Dresden, Germany; Mendez, Ivar; Victoria General Hospital, Halifax, Nova Scotia, Canada; Bernstein, Mark, The Toronto Hospital, Toronto, Ontario, Canada; Quigley, Mathew, Alleghemy University of Health Sciences, Pittsburgh, Pennsylvania; Payner, Troy; Indianapolis Surgical Group, Indianapolis, Indiana; Kulvik, Martti; Helsinki University Central Hospital, Helsinki, Finland; Seiler, Rolf W.; University Hospital, Bern, Switzerland; Weiss, Martin Harvey; University of Southern California, Department of Neurosurgery, Los Angeles, California; Fick, James R.; Medical College of Georgia, Department of Surgery, Augusta, Georgia; Leblanc, Richand; Montreal Neurological Institute, Montreal, Quebec, Canada; Buchfelder, Michael; Neurochirurgische Klinik mit Poliklinik der Universtat Erlangen-Nurnberg, Erlangen, Germany; Brotchi, Jacques; Hopital Erasme, Neruosergery, Cliniques Universiaites de Bruxelles, Bruxelles, Belgium; Astrup, Jens; Arhus Kommunehospital, Arhus C, Denmark; Henriksson, Roger; University Hospital, Umea, Sweden; Maciunas, Robert J.; Vanderbilt University Medical Center, Nashville, Tennessee; Ram, Zvi; The Chaim Sheba Medical Center; Tel-Hashomer, Israel; Andrews, David; Thomas Jefferson University Hospita, Philadelphia, Pennsylvania; Verlooy, Jan; University Hospital Antwerp; Antwerp, Belgium; Stockhammer, Gunther; Universitatsklinik fur Neurologie, Innsbruck, Austria; Favrot, Marie; Centre Leon Berard, Lyon, France; and Finocchiaro, Gaetano; Unita Neuroncologia Molecolare e Terapia Genica, Istituto Nazionale Neurologico Carlo Besta, Milano Mi Italy; *Prospective, Open-Label, Parallel-Group, Randomized Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previously Untreated Glioblastoma.* Sponsor: Genetic Therapy, Inc./Novartis

Sole FDA Review Recommended by NIH/ORDA: 8-22-96

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9608-158 (Open) Gene Therapy/Phase I-IB/Cancer/Melanoma or Sarcoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Plasmid DNA/Particle Mediated Gene Transfer (Accell®)/Cytokine/GM-CSF cDNA/Subcutaneous Injection

Mahvi, David M.; University of Wisconsin Hospital and Clinics Comprehensive Cancer Center, Madison, Wisconsin; *Phase I/IB Study of Immunization with Autologous Tumor Cells Transfected with the GM-CSF Gene by Particle-Mediated Transfer in Patients with Melanoma or Sarcoma.*

Sole FDA Review Recommended by NIH/ORDA: 8-26-96

9605-159 (Open) Gene Marking/Cancer/Pediatric Malignancies/In Vitro/CD34+ Autologous Bone Marrow and Peripheral Blood/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Heslop, Helen E.; Brenner, Malcolm K.; Krance, Robert A.; Baylor College of Medicine, Houston, Texas; *A Comparative Evaluation of the Utility of Hemopoietic Progenitor Cells Derived from Peripheral Blood vs Bone Marrow.*

Sole FDA Review Recommended by NIH/ORDA: 5-15-96

9609-160 (Open) Gene Therapy/Phase I/Cancer/Prostate Adenocarcinoma/Immunotherapy/In Vivo/Vaccination/Vaccinia Virus/Prostate Specific Antigen/Intradermal Injection

Kufe, Donald W.; and Eder, Joseph Paul; Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Trial Of Recombinant Vaccinia Virus That Expresses PSA In Patients With Adenocarcinoma Of The Prostate.*

Sole FDA Review Recommended by NIH/ORDA: 9-18-96

9609-161 (Closed) Gene Therapy/Phase I/Cancer/Small Cell Lung Cancer/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin(Gibco BRL)/B7-1(CD80) cDNA/Subcutaneous Injection

Antonia, Scott J.; H. Lee Moffitt Cancer Center, Tampa, Florida; *Treatment of Small Cell Lung Cancer Patients In Partial Remission Or At Relapse With B7-1 Gene-Modified Autologous Tumor Cells As A Vaccine With Systemic Interferon Gamma.*

Sole FDA Review Recommended by NIH/ORDA: 10-10-96
Closed: 1-23-98. Protocol Never Initiated

9610-162 (Open) Gene Therapy/Phase I/Cancer/Solid Tumors/Oncogene Regulation/HER-2/neu/ In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intratumoral Injection

LaFollette, Suzanne; Rush/Presbyterian/St. Luke's Medical Center, Chicago, Illinois; Murray, James L.; M.D. Anderson Cancer Center, Houston, Texas; Yoo, George; Wayne State University, Detroit, Michigan; *A Phase I Multicenter Study of Intratumoral E1A Gene Therapy for Patients with Unresectable or Metastatic Solid Tumors that Overexpress HER-2/neu.* Sponsor: Targeted Genetics Corporation

Sole FDA Review Recommended by NIH/ORDA: 10-29-96

9610-163 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/MART-1 Melanoma Antigen/Intramuscular Injection

Rosenberg, Steven A.; NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding The MART-1 Melanoma Antigen.*

Sole FDA Review Recommended by NIH/ORDA: 5-23-96

9610-164 (Closed) Gene Therapy/Phase I/Cancer/Liver(Hepatic)Metastases/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Sung, Max W.; and Woo, Savio L.C.; Mount Sinai Medical Center, New York, New York; *Phase I Trial of Adenoviral Vector Delivery of the Herpes Simplex Thymidine Kinase Gene by Intratumoral Injection Followed by Intravenous Ganciclovir in Patients with Hepatic Metastases.*

Sole FDA Review Recommended by NIH/ORDA: 11-12-96

9611-165 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/gp100 Melanoma Antigen/Intramuscular Injection

Rosenberg, Steven A.; NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding the GP100 Melanoma Antigen.*

NIH/ORDA Receipt Date: 11-13-96 . Sole FDA Review Recommended: 1-17-96

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9611-166 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Vaccinia Virus/MART-1 Melanoma Antigen/Intramuscular Injection

Rosenberg, Steven A.; NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Vaccinia Virus Encoding the MART-1 Melanoma Antigen.*

NIH/ORDA Receipt Date: 11-13-96. Sole FDA Review Recommended: 1-17-96

9611-167 (Closed) Gene Therapy/Phase II/Cancer/Glioblastoma/Pro-Drug/In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Maria, Bernard, *et al.* (All #9608-157 sites are eligible to participate in this study.) *Prospective, Open-Label, Multicenter, Extension Trial for the Treatment of Recurrent Glioblastoma Multiforme with Surgery and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir for Patients with Disease Progression Following Standard Treatment on Protocol GTI-0115.* Sponsor: Genetic Therapy, Inc./Novartis
This protocol is an extension of #9608-157.

NIH/ORDA Receipt Date: 11-13-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97

9611-168 (Closed) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Hersh, Evan M.; Arizona Cancer Center, Tucson, Arizona; Klasa, Richard; British Columbia Cancer Agency, Vancouver, B.C., Canada; Gonzales, Rene; University of Colorado Cancer Center, Denver, Colorado; Silver, Gary; Northern California Melanoma Clinic, San Francisco, California; Thompson, John A.; U. of Washington Medical Center, Seattle, Washington; *Phase II Study of Immunotherapy of Metastatic Melanoma by Direct Gene Transfer.* Sponsor: Vical, Incorporated

NIH/ORDA Receipt Date: 11-26-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97

9611-169 (Closed) Gene Therapy/Phase I/II/Cancer/Solid Tumors/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1102/Cytokine/Interleukin-2 cDNA/Direct Intratumoral Injection

Hersh, Evan, M.; Arizona Cancer Center, Tucson, Arizona; Rinehart, John; Scott and White Clinic, Temple, Texas; Rubin, Joseph; Mayo Clinic, Rochester, Minnesota; Sondak, Vernon K.; University of Michigan Medical Center, Ann Arbor, Michigan; Gonzales, Rene; University of Colorado Cancer Center, Denver, Colorado; Sobol, Robert E.; Sharp HealthCare, San Diego, California; and Forscher, Charles A.; Cedars-Sinai Comprehensive Cancer Center, Los Angeles, California; *Phase I/II Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Cancer by Direct Gene Transfer.* Sponsor: Vical, Incorporated

NIH/ORDA Receipt Date: 11-26-96. Sole FDA Review Recommended by NIH/ORDA: 1-17-97

9612-170 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Lung and Nasal Epithelial Cells/Cationic Liposome Complex/DOPE/CFTR cDNA/Aerosol Administration

Sorscher, Eric; University of Alabama, Birmingham, Medical Center; *Safety and Efficiency of Gene Transfer of Aerosol Administration of a Single Dose of a Cationic Lipid/DNA Formulation to the Lungs and Nose of Patients with Cystic Fibrosis.* Sponsor: Genzyme Corporation

NIH/ORDA Receipt Date: 12-17-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97

9701-171 (Open) Non-Therapeutic/In Vivo/Intradermal Cells/Adenovirus/Serotype 5/E. coli Cytosine Deaminase/Intradermal Injection

Harvey, Ben-Gary; and Crystal, Ronald G.; Rockefeller University Hospital, New York, New York; *Immune Response to Intradermal Administration of an Adenovirus Type 5 Gene Transfer Vector ($Ad_{GV}CD.10$) in Normal Individuals.*

NIH/ORDA Receipt Date: 1-9-97. *RAC Recommends Approval: 3-6-97/NIH Approval: 4-21-97

9701-172 (Closed) Gene Therapy/Phase I/Cancer/Germ Cell Tumors (Testicular Cancer)/Chemoprotection/In Vitro/G-CSF Mobilized Autologous CD34+ Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Bone Marrow Transplant

Cornetta, Kenneth; and Abonour, Rafat; Indiana University Department of Medicine, Indianapolis, Indiana; *High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study.*

NIH/ORDA Receipt Date: 1-9-97. Sole FDA Review Recommended by NIH/ORDA: 2-26-97

Closed to patient accrual: 3-15-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9701-173 (Closed) Gene Therapy/Phase I/Cancer/Brain Tumors/Chemoprotection/In Vitro/Peripheral Blood CD34+ Cells/Retrovirus/O^6-Methylguanine DNA Methyltransferase cDNA/Intravenous Infusion

Croop, James; Indiana University School of Medicine, Indianapolis, Indiana; and Kieran, Mark, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine(PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^6-Methylguanine DNA Methyltransferase.*

NIH/ORDA Receipt Date: 1-13-97. Sole FDA Review Recommended by NIH/ORDA: 2-4-97

Notification that trial is closed to new research participant enrollment: 2-20-01

9701-174 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Interleukin-2 cDNA/Neomycin Phosphotransferase cDNA/Immunoisolation Device/Subcutaneous Implantation

Das Gupta, Tapas K.; University of Illinois at Chicago, Chicago, Illinois; *A Pilot Study Using Interleukin-2 Transfected Irradiated Allogeneic Melanoma Cells Encapsulated in an Immunoisolation Device In Patients with Metastatic Malignant Melanoma.*

NIH/ORDA Receipt Date: 1-13-97. Sole FDA Review Recommended by NIH/ORDA: 2-21-97

9701-175 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Stereotactic Injection

Lieberman, Frank; Germano, Isabelle; and Woo, Savio; Mount Sinai Medical Center, New York, New York; *Gene Therapy for Recurrent Glioblastoma Multiforme: Phase I Trial of Intraparenchymal Adenoviral Vector Delivery of the HSV-TK Gene and Intravenous Administration of Ganciclovir.*

NIH/ORDA Receipt Date: 1-22-97. Sole FDA Review Recommended by NIH/ORDA: 2-12-97

9702-176 (Open) Gene Therapy/Phase I/II/Cancer/Prostate Adenocarcinoma/Immunotherapy/In Vivo/Vaccination/Vaccinia Virus/Prostate Specific Antigen/Intradermal Injection

Sanda, Martin G.; University of Michigan Urology Clinics, Ann Arbor, Michigan; *A Phase I/II Clinical Trial Evaluating the Safety and Biological Activity of Recombinant Vaccinia-PSA Vaccine in Patients with Serological Recurrence of Prostate Cancer Following Radical Prostatectomy.*

NIH/ORDA Receipt Date: 2-19-97. Sole FDA Review Recommended by NIH/ORDA: 5-13-97

9702-177 (Open) Gene Marking/Cancer/Chronic Myelogenous Leukemia/In Vitro/Autologous Peripheral Blood Cells Mobilized by Cyclophosphamide and G-CSF/Retrovirus/Neomycin Phosphotransferase cDNA/Autologous Bone Marrow Transplant

Verfaille, Catherine; McIvor, Scott; McCullough, Jeff; and McGlave, Philip; University of Minnesota, Minneapolis, Minnesota; *Autologous Marrow Transplantation for Chronic Myelogenous Leukemia Using Retrovirally Marked Peripheral Blood Progenitor Cells Obtained after In Vivo Cyclophosphamide/G-CSF Priming.*

NIH/ORDA Receipt Date: 2-21-97. Sole FDA Review Recommended by NIH/ORDA: 3-14-97

9703-178 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD34+ Autologous Cord Blood Cells/Retrovirus/Transdominant Trev/Intravenous

Belmont, John W.; Texas Children's Hospital, Houston, Texas; *Phase I Clinical Trial of TREV Gene Therapy for Pediatric AIDS.*

NIH/ORDA Receipt Date: 3-10-97. Sole FDA Review Recommended by NIH/ORDA: 3-31-97

9703-179 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Carcinoembryonic Antigen/Intravenous

Lyerly, Kim H.; Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Active Immunotherapy With Carcinoembryonic Antigen RNA-Pulsed Autologous Human Cultured Dendritic Cells In Patients with Metastatic Malignancies Expressing Carcinoembryonic Antigen.*

NIH/ORDA Receipt Date: 3-14-97. Publicly Reviewed at the June 1997 RAC meeting.

Sole FDA Review Recommended by NIH/ORDA: 6-24-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9703-180 (Open) Gene Therapy/Phase I/Other/Cubital Tunnel Syndrome/In Vivo/Autologous Muscle Cells/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Human Insulin-Like Growth Factor-1(hIGF-1)/Intramuscular Injection

Netscher, David; Hand Clinic at the Veteran's Affairs (VA) Medical Center, Houston, Texas; *Phase I Single Dose-Ranging Study Of Formulated hIGF-1 Plasmid In Subjects With Cubital Tunnel Syndrome.* Sponsor: Gene Medicine, Inc.

NIH/ORDA Receipt Date: 3-17-97. Sole FDA Review Recommended: 4-7-97

9703-181 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD8 + and CD4+ T Lymphocytes/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous/Concurrent Interleukin-2 Therapy

Connick, Elizabeth; University of Colorado Health Sciences Center, Denver, Colorado; Deeks, Steven G.; University of California, San Francisco General Hospital, San Francisco, California; Scadden, David; Massachusetts General Hospital (East), Charlestown, Massachusetts; Mitsuyasu, Ronald; University of California, Los Angeles Medical Center, Los Angeles, California; *A Phase II Study of the Activity and Safety of Autologous CD4-Zeta Gene-Modified T Cells With or Without Exogenous Interleukin-2 in HIV Infected Patients.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 3-19-97. Sole FDA Review Recommended: 4-18-97

Notification from sponsor that trial is closed: 4-09-01

9703-182 (Open) Gene Therapy/Phase II/Monogenic Inherited Disorder/Cystic Fibrosis/Sinusitis/Correction/In Vivo/Maxillary Sinus Epithelial Cells/ Adeno-associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Maxillary Sinus Administration

Gardner, Phyllis; Stanford University's General Clinical Research Center (GCRC), Palo Alto, California; *A Phase I/II Study of tgAAVCF for the Treatment of Chronic Sinusitis With Cystic Fibrosis.* Sponsor: Targeted Genetics Corporation

NIH/ORDA Receipt Date: 3-13-97. Sole FDA Review Recommended: 4-1-97

9703-183 (Closed) Gene Marking/Cancer/EBV-Positive Hodgkin Disease/In Vitro/EBV-Specific Hodgkin Disease/In Vitro/EBV-Specific Cytotoxic Lymphocytes/Retrovirus/Neomycin Phosphotransferase/Bone Marrow Transplant

Straus, Stephan E.; National Institutes of Health, Bethesda, Maryland; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T-Lymphocytes To Patients With Relapsed EBV-Positive Hodgkin Disease.*
Compassionate Case

NIH/ORDA Receipt Date: 3-19-97. Sole FDA Review Recommended by NIH/ORDA: 3-25-97

Patient never treated (closed as of 11-18-97)

9703-184 (Closed) Gene Therapy/Phase I/Cancer/Prostate Cancer/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1102/Cytokine/Interleukin-2 cDNA/Intratumoral Injection

Belldegrun, Arie; University of California, Los Angeles, School of Medicine, Los Angeles, California; *A Phase I Study Evaluating the Safety and Efficacy of Interleukin-2 Gene Therapy Delivered by Lipid Mediated Gene Transfer (Leuvectin) in Prostate Cancer Patients.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 3-24-97. Sole FDA Review Recommended by NIH/ORDA: 5-21-97

9704-185 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Melanoma Cell/Canarypox Virus/Cytokine/Interleukin-12 cDNA/Intratumoral Injection

Conry, Robert M.; University of Alabama at Birmingham, Birmingham, Alabama; *Phase Ib Trial of Intratumoral Injection of a Recombinant Canarypox Virus Encoding the Human Interleukin-12 Gene (ALVAC-hIL-12) in Patients with Surgically Incurable Melanoma* Sponsor: NCI- Cancer Therapy Evaluation Program

NIH/ORDA Receipt Date: 4-1-97. Sole FDA Review Recommended by NIH/ORDA: 7-2-97

9704-186 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Nasal Epithelial Cells/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Cationic Liposome Complex/EDMPC/Intranasal Administration

Noone, Peadar G.; Knowles, Michael R.; University of North Carolina at Chapel Hill, North Carolina; *A Double-Blind, Placebo Controlled, Dose Ranging Study to Evaluate the Safety and Biological Efficacy of the Lipid-DNA Complex GR213487B in the Nasal Epithelium of Adult Patients with Cystic Fibrosis.* Sponsor: Glaxo Wellcome Inc.

NIH/ORDA Receipt Date: 4-23-97. Sole FDA Review Recommended by NIH/ORDA: 5-13-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9705-187 (Closed) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug/In Vivo/AutologousTumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Hall, Simon J.; Woo, Savio L.C.; Mount Sinai School of Medicine, New York, New York; *Phase I Trial of Adenoviral-Mediated Herpes Simplex Thymidine Kinase Gene Transduction in Conjunction with Ganciclovir Therapy as Neo-adjuvant Treatment for Patients with Clinically Localized (Stage T1c and T2b&c) Prostate Cancer Prior to Radical Prostatectomy.*

NIH/ORDA Receipt Date: 5-7-97. Sole FDA Review Recommended by NIH/ORDA: 5-28-97
Closed to accrual: 11-12-01

9705-188 (Open) Gene Therapy/Phase I/Cancer/Chronic Myelogenous Leukemia/Chemoprotection/Tyr-22 Murine Dihydrofolate Reductase Gene/Antisense/Anti-b3a2BCR/ABL Gene/In Vitro/Autologous Peripheral Blood CD34+ Cells Mobilized by Cyclophosphamide and G-CSF/Retrovirus/Autologous Bone Marrow Transplant

Verfaillie, Catherine; McIvor, Scott; McCullough, Jeff; McGlave, Philip; University of Minnesota, Minneapolis, Minnesota; *Autologous Transplantation for Chronic Myelogenous Leukemia with Stem Cells Transduced with a Methotrexate Resistant DHFR and Anti-BCR/ABL Containing Vector and Post Transplant Methotrexate Administration.*

NIH/ORDA Receipt Date: 5-16-97. Sole FDA Review Recommended by NIH/ORDA: 6-6-97

9705-189 (Closed) Gene Therapy/Phase I/Cancer/Hepatocellular Carcinoma/Tumor Suppressor Gene/In Vivo/Autologous nTumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Belani, Chandra P.; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; *Phase I Study of Percutaneous Injections of Adenovirus p53 Construct (Adeno-p53) for Hepatocellular Carcinoma.*

NIH/ORDA Receipt Date: 5-27-97. Sole FDA Review Recommended by NIH/ORDA: 9-19-97

Closed: 3-7-00

9705-190 (Open) Gene Therapy/Phase I/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DOTMA-Cholesterol/Cytokine/Interleukin-2 cDNA/Intratumoral Injection

O'Malley, Bert W.; Johns Hopkins Medical Institutions, Baltimore, Maryland; *A Double-Blind, Placebo-Controlled, Single Rising-Dose Study of the Safety and Tolerability of Formulated hIL-2 Plasmid in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Gene Medicine, Inc.

NIH/ORDA Receipt Date: 5-27-97. Sole FDA Review Recommended by NIH/ORDA: 6-16-97

9706-191 (Closed) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Gluckman, Jack L..; Gleich, Lyon L., University of Cincinnati Medical Center, Cincinnati, Ohio; Swinehart, James M.; Colorado Medical Research Center, Denver, Colorado; Hanna, Ehab; University of Arkansas for Medical Sciences/Arkansas Cancer Research Center (UAMS), Little Rock, Arkansas; Castro, Dan J.; University of California, Los Angeles, Los Angeles, California; Gapany, Markus; Veterans Affairs Medical Center, Minneapolis, Minnesota; Carroll, William R.; University of Alabama at Birmingham, Birmingham, Alabama; Coltrera, Marc D.; University of Washington Medical Center, Seattle, Washington; Wolf, Gregory T.; University of Michigan Medical Center, Ann Arbor, Michigan; and Okuno, Scott; Mayo Clinic, Rochester, Minnesota; *Phase II Study of Immunotherapy by Direct Gene Transfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 6-6-97. Sole FDA Review Recommended by NIH/ORDA: 7-7-97

9706-192 (Open) Gene Therapy/Phase I/Cancer/Prostate/Tumor suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Belldegrun, Arie; and Figlin, Robert.; UCLA School of Medicine, Los Angeles, California; *A Phase I Study in Patients with Locally Advanced or Recurrent Adenocarcinoma of the Prostate Using SCH58500 (rAd/p53) Administered by Intratumoral Injection.* Sponsor: Schering-Plough Corporation

NIH/ORDA Receipt Date: 6-9-97. Sole FDA Review Recommended by NIH/ORDA: 9-17-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9706-193 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/CEA-Expressing Malignancies/In Vivo/Autologous Muscle Cells/Canarypox Virus/Vaccinia Virus/Carcinoembryonic Antigen cDNA/Intramuscular and Percutaneous Injection

Marshall, John L.; Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C.; *A Pilot Study of Sequential Vaccinations with ALVAC-CEA and Vaccinia-CEA with the Addition of IL-2 and GM-CSF in Patients with CEA Expressing Tumors.* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-18-97. Sole FDA Review Recommended by NIH/ORDA: 9-18-97

9706-194 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy/In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1 IIIB Envelope Protein/Intramuscular Injection

Aboulafia, David; Virginia Mason Clinic, Seattle, Washington; Campbell, Thomas; University of Colorado Health Sciences Center, Denver, Colorado; Kumar, Princy; Georgetown University Medical Center, Washington, D.C.; Murphy, Robert; Northwestern University Medical School, Chicago, Illinois; Skolnik, Paul; New England Medical Center, Boston, Massachusetts; and Wheat, Joseph; Indiana University Hospital, Indianapolis, Indiana; *A Phase II, Randomized, Double Blind Placebo Controlled Study of Combination Drug Anti-Retroviral Therapy to Include a Reverse Transcriptase Inhibitor and a Protease Inhibitor Plus HIV-IT(V) or Placebo in HIV Patients with CD4+ Counts $\geq$ 100, and HIV RNA $\geq$ 1K, and $\leq$ 10K.* Sponsor: Chiron Corporation

NIH/ORDA Receipt Date: 6-23-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97
5-10-00: IND no longer active

9706-195 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/CEA-Expressing Malignancies/In Vivo/Vaccinia Virus/Carcinoembryonic Antigen cDNA/Intradermal and Subcutaneous Injections

Conry, Robert M.; The University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Trial of a Recombinant Vaccinia-CEA (180 Kd) Vaccine Delivered by Intradermal Needle Injection Versus Subcutaneous Jet Injection in Patients with Metastatic CEA-Expressing Adenocarcinoma.* Sponsor: Drug Regulatory Affairs Branch, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment, Diagnosis and Centers, NCI, NIH

NIH/ORDA Receipt Date: 6-26-97. Sole FDA Review Recommended by NIH/ORDA: 9-5-97

9706-196 (Open) Gene Therapy/Phase I/Monogenic Disease/Chronic Granulomatous Disease/In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/gp91phox/Intravenous Infusion

Croop, James; Indiana University School of Medicine, Indianapolis, Indiana; *Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study.*

NIH/ORDA Receipt Date: 6-30-97. Sole FDA Review Recommended by NIH/ORDA: 7-21-97

9706-197 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Melanoma Cell/Canarypox Virus/B7(CD80)/Interleukin-12/Cytokine/Intratumoral Injection

Conry, Robert M.; University of Alabama at Birmingham, Birmingham, Alabama; *Phase Ib Trial of Intratumoral Injection of a Recombinant Canarypox Virus Encoding Human B7.1 (ALVAC-hB7.1) or a Combination of ALVAC-hB7.1 and a Recombinant Canarypox Virus Encoding Human Interleukin-12 (ALVAC-hIL-12) in Patients with Surgically Incurable Melanoma.* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-30-97. Sole FDA Review Recommended by NIH/ORDA: 9-5-97

9707-198 (Closed) Gene Therapy/Phase I/II/Cancer/Colorectal Carcinoma Expressing TAG-72/In Vitro/Autologous CD8+ and CD4+ T Lymphocytes/Retrovirus/CC49-Zeta T Cell Receptor/Intravenous Infusion

Venook, Alan and Warren, Robert S.; University of California, San Francisco, California and Fisher, George; Stanford University, Palo Alto, California; *A Phase I/II Study of Autologous CC49-Zeta Gene-Modified T Cells and α-Interferon in Patients with Advanced Colorectal Carcinomas Expressing the Tumor-Associated Antigen, TAG-72.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 7-7-97. Sole FDA Review Recommended by NIH/ORDA: 8-28-97

Notification from sponsor that trial is closed: 4-09-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9707-199 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Breast/Head and Neck Cancer/Cutaneous T-Cell Lymphoma/Immunotherapy/In Vitro/Autologous Fibroblasts/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-12/Intratumoral Injection

Park, Chan H.; Samsung Medical Center, Seoul, Korea; Kim, Sunyoung; Seoul National University, Seoul, Korea; Lotze, Michael; Tahara, Hideaki; and Robbins, Paul; University of Pittsburgh, Pittsburgh, Pennsylvania; *IL-12 Gene Therapy Using Direct Injection of Tumors with Genetically Engineered Autologous Fibroblasts.*

NIH/ORDA Receipt Date: 7-22-97. Sole FDA Review Recommended by NIH/ORDA: 10-30-97

9707-200 (Open) Gene Therapy/Phase I/II/Cancer/Non-Hodgkin's B-Cell Lymphoma/Mantle Cell Lymphoma/Immunotherapy/In Vivo/Naked Plasmid DNA/Tumor Idiotype/Intramuscular Injection

Levy, Ronald; Stanford University School of Medicine, Stanford, California; *A Phase I/II Study of Vaccine Therapy for B-Cell Lymphoma Utilizing Plasmid DNA Coding for Tumor Idiotype.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 7-24-97. Sole FDA Review Recommended by NIH/ORDA: 8-13-97

9707-201 (Open) Gene Therapy/Phase I/ Cancer/Ovarian/Immunotherapy/In Vitro/Autologous Tumor Cells/Canarypox Virus/B7.1 (CD80)/Intraperitoneal Injection

Freedman, Ralph; The University of Texas, M.D. Anderson Cancer Center, Houston, Texas; *Intraperitoneal (IP) Autologous Therapeutic Tumor Vaccine (AUT-OV-ALVAC-hB7.1) plus IP rIFN-γ for Patients with Ovarian Cancer. A Pilot Study.* Sponsor: NCI Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-202 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Melanoma/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Dranoff, Glenn and Soiffer, Robert; Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Lethally Irradiated Melanoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.*

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-203 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Non-Small Cell Lung Carcinoma (NSCLC)/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Dranoff, Glenn and Salgia, Ravi; Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Lethally Irradiated Non-Small Cell Lung Carcinoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.*

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-204 (Closed) Gene Therapy/Phase I/Monogenic Disease/Leukocyte Adherence Deficiency (LAD)/In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/CD18/Intravenous Infusion

Hickstein, Dennis and Bauer, Thomas R. National Institutes of Health, Bethesda, Maryland; *Retrovirus-Mediated Transfer of the cDNA for Human CD18 into Peripheral Blood Repopulating Cells of Patients with Leukocyte Adherence Deficiency.*

NIH/ORDA Receipt Date: 7-31-97. Sole FDA Review Recommended by NIH/ORDA: 9-17-97
Closed: 9-17-00

9708-205 (Closed) Gene Therapy/Phase I/II/Cancer/Prostate/Immunotherapy/ In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Simons, Jonathan W.; Johns Hopkins Oncology Center, Baltimore, Maryland; *Phase I/II Study of Allogeneic Human GM-CSF Gene Transduced Irradiated Prostate Cancer Cell Vaccines in Patients with Prostate Cancer.*

NIH/ORDA Receipt Date: 8-19-97. Sole FDA Review Recommended by NIH/ORDA: 9-9-97

Closed: 7-23-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9708-206 (Closed) Gene Therapy/Phase I/II/Cancer/Chronic Myelogenous Leukemia/Adoptive Immunotherapy/In Vitro/Donor CD8+ and CD4+ Lymphocytes/Retrovirus/Hygromycin Phosphotransferase-Herpes Simplex Thymidine Kinase Fusion Gene/Intravenous Infusion

Flowers, Mary E. D. and Riddell, Stanley; Fred Hutchinson Cancer Research Center, Seattle, Washington; *Infusion of Polyclonal HyTK (hygromycin phosphotransferase and HSV thymidine kinase gene)-transduced Donor T Cells for Adoptive Immunotherapy in Patients with Relapsed CML after Allogeneic Stem Cell Transplant: Phase I-II Clinical Trial.*

NIH/ORDA Receipt Date: 8-19-97. Sole FDA Review Recommended by NIH/ORDA: 9-26-97
Closed to new accrual: 4-24-00.

9708-207 (Closed) Gene Therapy/Phase I/Cancer/Colorectal/Immunotherapy/In Vivo/Autologous Tumor Cells/Canarypox Virus/Carcinoembryonic Antigen/B7.1 (CD80)/Intradermal Scarification

Kaufman, Howard L.; Albert Einstein Cancer Center, Bronx, New York; *Phase I Clinical Trial of a Recombinant ALVAC-CEA-B7 Vaccine in the Treatment of Advanced Colorectal Carcinoma.* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 8-21-97. Sole FDA Review Recommended by NIH/ORDA: 11-25-97
Closed: 2-99.

9708-208 (Open) Gene Therapy/Phase I/Cancer/Mesothelioma/Pro-Drug/In Vivo/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Herpes Simplex Virus Thymidine Kinase/Ganciclovir/Intrapleural Administration

Schwarzenberger, Paul; Louisiana State University Medical Center, New Orleans, Louisiana; *The Treatment of Malignant Pleural Mesothelioma with a Gene-Modified Cancer Vaccine: A Phase I Study.*

NIH/ORDA Receipt Date: 8-25-97. Sole FDA Review Recommended by NIH/ORDA: 9-16-97

9708-209 (Closed) Non-Therapeutic/In Vivo/Bronchial Epithelial Cells/Adenovirus/Serotype 5/*E. coli* Cytosine Deaminase/Intrabronchial Administration

Harvey, Ben-Gary and Crystal, Ronald G.; Rockefeller University Hospital, New York, New York; *Systemic and Respiratory Immune Response to Administration of an Adenovirus Type 5 Gene Transfer Vector ($Ad_{GV}CD.10$).*

NIH/ORDA Receipt Date: 8-26-97. Publicly Reviewed at the December 16, 1997 RAC meeting
Closed: 09-19-00

9709-210 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/β2-Macroglobulin cDNA/Direct Intratumoral Injection

Gonzales, Rene; University of Colorado Cancer Center, Denver, Colorado; Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; Deisseroth, Albert, Yale University, New Haven, Connecticut; Paciucci, Paolo A., Mt. Sinai Medical Center, New York, New York; Hutchins, Laura F., University of Arkansas for Medical Sciences, Little Rock, Arkansas; Galanis, Evanthia, Mayo Clinic, Rochester, Minnesota; Schaefer, Paul L., Toledo Clinic, Toledo, Ohio; Amatruda, Thomas, Virginia Piper Cancer Institute Abbott Northwestern Hospital, Minneapolis, Minnesota; Kuzel, Timothy, Northwestern Medical Faculty Foundation Northwestern Memorial Hospital, Chicago, Illinois; Blum, Ronald H., Beth Israel Medical Center, Phillips Ambulatory Care Center, New York, New York; Whitman, Eric D., The Melanoma Center of St. Louis, Saint Louis, Missouri; Cobb, Patrick, Billings Interhospital Oncology Project, Billings, Montana; Amin, Bipinkumar, Mid Dakota Clinic, Bismarck, North Dakota; Chowhan, Naveed, Cancer Care Center Incorporated, New Albany, Indiana; Lutzky, Jose, Mount Sinai Medical Center, Miami, Florida; Amatruda, Thomas, North Memorial Healthcare, Hubert H. Humphrey Cancer Center, Robbinsdale, Minnesota ;Patel, Ravi, Comprehensive Blood and Cancer Center, Bakersfield, California; Dobbs, Tracy W., Baptist Hospital of East Tennessee, Knoxville, Tennessee; Ahmed, Fakhiuddin, HemOnCare, P.C., Brooklyn, New York; Thant, Myo, Maryland Hematology/Oncology Associates, Baltimore, Maryland; Stark, James J., Maryview Medical Center, Portsmouth, Virginia; Arena, Francis, Arena Oncology Associates, Great Neck, New York; Soori, Gamini, Alegent Health, Bergan Mercy Medical Center, Omaha, Nebraska; Samlowski, Wolfram, University of Utah Health Sciences Center; Huntsman Cancer Institute, Salt Lake City, Utah; Polikoff, Jonathan A., Kaiser Permanente Medical Group, San Diego, California; Hawkins, Michael, Washington Hospital Center, Washington Cancer Institute, Washington, D.C.; Richart, John, Saint Louis University Health Sciences Center, St. Louis, Missouri; Patel, Taral, Columbus, Community Clinical Oncology Program, Columbus, Ohio; Levine, Edward, Wake Forest University School of Medicine, Winston Salem, North Carolina; Richards, Jon, Lutheran General Hospital, Park Ridge, Illinois; and Thompson, John A., University of Washington Medical Center, Seattle, Washington; *Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 9-8-97. Sole FDA Review Recommended by NIH/ORDA: 9-26-97

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9708-211 (Open) Gene Therapy/Phase I/Monogenetic Disease/Canavan Disease/In Vivo/Autologous Brain Cells/Plasmid DNA/Adeno-associated Virus/Poly-L-Lysine/Cationic Liposome Complex/DC-Chol/DOPE/Aspartoacylase cDNA/Intracranial (Ommaya Reservoir) Administration

Seashore, Margretta R.; Yale University, New Haven, Connecticut; *Gene Therapy of Canavan Disease: Retreatment of Previously Treated Children.*

NIH/ORDA Receipt Date: 8-28-97. Publicly Reviewed at the December 16, 1997 RAC meeting

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9709-212 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Vical-1102/Interleukin-2 cDNA/Intratumoral Injection

Gonzalez, Rene; University of Colorado Health Sciences Center, Denver, Colorado; Hersh, Evan M.; Arizona Cancer Center, Tucson, Arizona; Rubin, Joseph; Mayo Clinic, Rochester, Minnesota; and Thompson, John A.; University of Washington Medical Center, Seattle, Washington; *Phase I Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) with IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Melanoma.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 9-18-97. Sole FDA Review Recommended by NIH/ORDA: 10-8-97

9709-213 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD8+ T Cells/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous

Deeks, Steven G.; University of California, San Francisco General Hospital, San Francisco, California; *A Phase II Study of Autologous CD4-Zeta Gene-Modified T Cells in HIV-Infected Patients with Undetectable Plasma Viremia on Combination Antiretroviral Drug Therapy.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 9-22-97. Sole FDA Review Recommended by NIH/ORDA: 10-10-97

Study closed to new accrual, follow-up is continuing: 7-13-01

9709-214 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53

Breau, Randall L.; University of Arkansas for Medical Sciences, Little Rock, Arkansas; Clayman, Gary L.; The University of Texas MD Anderson Cancer Center, Houston, Texas; Yoo, George H.; Wayne State University/Barbara Ann Karmanos Cancer Institute, Detroit, Michigan; Medina, Jesus E.; University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; Murphy, Barbara S.; Vanderbilt University Medical Center, Nashville, Tennessee; Goodwin, W. Jarrard; University of Miami Hospitals and Clinics, Miami, Florida; Weber, Jeffery S.; University of Southern California, Los Angeles, California; Schuller, David E.; Ohio State University Medical Center, Columbus, Ohio; Bukowski, Ronald M.; The Cleveland Clinic Foundation, Cleveland, Ohio; Hamm, John; University of Louisville Health Sciences Center, Louisville, Kentucky; Agarwala, Sanjiv; University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; Hochster, Howard S.; New York University Medical Center, New York, New York; Dietz, Andreas; University of Heidelberg, Heidelberg, Germany; Eβer, Dirk; Ear, Nose and Throat Clinic, Erfurt, Germany; and Flood, William A.; Milton S. Hershey Medical Center, Hershey, Pennsylvania; *A Phase II Multi-Center, Open Label, Randomized Study to Evaluate Effectiveness and Safety of Two Treatment Regimens of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Aventis (formerly Gencell)

NIH/ORDA Receipt Date: 9-22-97. Sole FDA Review Recommended by NIH/ORDA: 10-21-97

9709-215 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vivo/Autologous Tumor Cells/Canarypox Virus/Carcinoembryonic Antigen/B7.1 (CD80)/Intramuscular and Intradermal Injections

von Mehren, Margaret; Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I/Pilot Study of ALVAC-CEA-B7.1 Immunization in Patients with Advanced Adenocarcinoma Expressing CEA.* Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 9-24-97. Sole FDA Review Recommended by NIH/ORDA: 10-28-97

9709-216 (Open) Gene Therapy/Phase I/Cancer/Breast/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Cutaneous or Subcutaneous

von Mehren, Margaret; Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I/Pilot Study of p53 Intralesional Gene Therapy with Chemotherapy in Breast Cancer .* Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 9-24-97. Sole FDA Review Recommended by NIH/ORDA: 10-28-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9710-217 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Logothetis, Christopher J.; University of Texas MD Anderson Cancer Center, Houston, Texas; *A Tolerance and Efficacy Study of Intraprostatic INGN 201 Followed by Pathological Staging and Possible Radical Prostatectomy in Patients with Locally Advanced Prostate Cancer.* Sponsor: Introgen Therapeutics, Inc.

NIH/ORDA Receipt Date: 10-3-97. Sole FDA Review Recommended by NIH/ORDA: 11-6-97

9710-218 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Hammerhead Ribozyme/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Tat and Rev Hammerhead Ribozyme/Intravenous

Krishnan, Amrita and Zaia, John, A.; City of Hope Medical Center, Duarte, California; *High Dose Chemotherapy and Autologous Peripheral Stem Cell Transplantation for HIV Lymphomas: A Phase IIa Study of Comparative Marking Using a Ribozyme Gene and a Neutral Gene.* Sponsor: Ribozyme Pharmaceuticals, Inc.

NIH/ORDA Receipt Date: 10-6-97. Sole FDA Review Recommended by NIH/ORDA: 10-27-97

9710-219 (Open) Gene Therapy/Phase I/Cancer/Bladder/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intravesical Administration

Pagliaro, Lance C.; The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I Trial of Intravesical Ad-p53 Treatment in Locally Advanced and Metastatic Bladder Cancer.*

NIH/ORDA Receipt Date: 10-21-97. Sole FDA Review Recommended by NIH/ORDA: 11-10-97

9710-220 (Open) Gene Therapy/Phase II/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Bronchoscopy or Percutaneous Intratumoral Injection

Dobbs, Tracy W.; East Tennessee Oncology/Hematology, P.C., Knoxville, Tennessee; *A Phase II Gene Therapy Study in Patients with Non-Small Cell Lung Cancer Using SCH 58500 (rAd/p53) in Combination with Chemotherapy for Multiple Cycles.* Sponsor: Schering Plough Research Institute

NIH/ORDA Receipt Date: 10-31-97. Not Selected for RAC Public Review: 12-15-97

9711-221 (Open) Gene Therapy/Phase I/Other/ Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Administration

Crystal, Ronald G.; The New York Hospital-Cornell Medical Center, New York, New York; *Phase I Study of Direct Administration of a Replication-Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Life Threatening Diffuse Coronary Artery Disease.* Sponsor: Parke-Davis Pharmaceutical Research.

NIH/ORDA Receipt Date: 11-4-97. Publicly Reviewed at the December 16, 1997 RAC meeting

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9711-222 (Open) Gene Therapy/Phase I/Monogenetic Disease/Canavan Disease/In Vivo/Autologous Brain Cells/Plasmid DNA/Adeno-Associated Virus/Protamine/Cationic Liposome Complex/DC-Cholesterol-DOPE/Aspartoacylase cDNA/Intracranial (Ommaya Reservoir)

Freese, Andrew; Thomas Jefferson University, Philadelphia, Pennsylvania; *Gene Therapy of Canavan Disease.*

NIH/ORDA Receipt Date: 11-12-97. Not Selected for RAC Public Review: 1-26-98

9712-223 (Open) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Allogeneic Neuroblastoma Cell Lines/Retrovirus/Cytokine/Interleukin-2 (IL-2)/Plasmid/Electroporation/Chemokine/Lymphotactin/Subcutaneous Injection

Hale, Gregory; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Chemokine and Cytokine Gene Modified Allogeneic Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using a Retroviral Vector.*

NIH/ORDA Receipt Date: 12-3-97. Not Selected for RAC Public Review: 12-29-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9712-224 (Open) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Autologous Tumor Cells (Non-Irradiated)/Type 5 Adenovirus/Cytokine/Interleukin-2 (IL-2)/Chemokine/Lymphotactin/Subcutaneous Injection

Hale, Gregory; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector.*

NIH/ORDA Receipt Date: 12-3-97. Not Selected for RAC Public Review: 12-29-97

9712-225 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/In Vitro/Antisense TAR/Transdominant Rev/Intravenous

Isola, Luis M.; Mount Sinai Medical Center, New York, New York; *A Phase I Trial of Autologous and Allogeneic Bone Marrow Transplantation with Genetically Marked Cells for the Treatment of HIV Associated Lymphoid Malignancies.*

NIH/ORDA Receipt Date: 12-15-97. Not Selected for RAC Public Review: 1-7-98
IND withdrawn: 4-4-00

9712-226 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injections

Dreicer, Robert; University of Iowa College of Medicine, Iowa City, Iowa; Simon, George R.; University of Colorado Health Sciences Center, Denver, Colorado; Williamson, Stephen; University of Kansas Medical Center, Kansas City, Kansas; VanEcho, David A.; University of Maryland School of Medicine, Baltimore, Maryland; Rosen, Fred; University of Illinois at Chicago Hospitals & Clinics; Endicott, James N.; University of South Florida, Tampa, Florida; Bier-Laning, Carol M.; University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; Minn, Heikki; Turku University Central Hospital, Turku Finland; Guertin, Louis; CHUM - Pavilion Notre-Dame, Montreal, Quebec; Liu, Fei-Fei; Princess Margaret Hospital, Toronto, Ontario; Wadler, Scott; Montefiore Medical Center, Albert Einstein College of Medicine; Bronx, New York; Goss, Glenwood D.; Ottawa Regional Cancer Centre, Ottawa, Ontario; Saarilanti, Kauko; Helsinki University Central Hospital, Helsinki Finland; Mudad, Raja; Tulane University Medical Center, New Orleans, Louisiana; Spiro, Jeffrey; University of Connecticut Health Center, Farmington, Connecticut; Zielinski, Christoph, University of Vienna; Link, Brian, University of Iowa Hospital and Clinics, Iowa City, Iowa; and Truelson, John, University of Texas Southwestern Medical School, Dallas, Texas; *A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Aventis (formerly Gencell)

NIH/ORDA Receipt Date: 12-17-97. Not Selected for RAC Public Review: 1-9-98

9801-227 (Closed) Gene Therapy/Phase II/Cancer/Melanoma/Head and Neck Cancer/Immunotherapy/In Vitro/Autologous Fibroblasts/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-12 cDNA/Neomycin Phosphotransferase cDNA/Intratumoral Injection

Lotze, Michael T.; University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; *IL-12 Gene Therapy Using Direct Injection of Tumors with Genetically Engineered Autologous Fibroblasts (A Phase II Study).*

NIH/ORDA Receipt Date: 1-2-98. Not Selected for RAC Public Review: 2-18-98
Protocol is terminated: 11-1-01

9801-228 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/In Vivo/ Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Acyclovir/Intraperitoneal Injection

Kieback, Dirk G.; Baylor College of Medicine, Houston, Texas; *Phase I Study of Concomitant Adenovirus-Mediated Transduction of Ovarian Cancer with HSV-tk Gene Followed by Intravenous Administration of Acyclovir and Chemotherapy with Topotecan in Patients after Optimal Debulking Surgery for Recurrent Ovarian Cancer.*

NIH/ORDA Receipt Date: 1-14-98. Not Selected for RAC Public Review: 2-5-98

9801-229 (Open) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Kadmon, Dov; Baylor College of Medicine, Houston, Texas; *Neoadjuvant Pre-radical Prostatectomy Gene Therapy (HSV-tk Gene Transduction Followed by Ganciclovir) in Patients with Poor Prognostic Indicators.*

NIH/ORDA Receipt Date: 1-16-98. Not Selected for RAC Public Review: 2-13-98

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9801-230 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/Antisense TAR/Antisense tat | rev/In Vitro/CD34+ Cells/Intravenous

Cowan, Morton J. and Conant, Marcus A.; University of California, San Francisco, San Francisco, California; *Evaluation of the Safety and Effects of Ex Vivo Modification and Re-infusion of CD34+ Cells by an Antisense Construct Against HIV-1 in a Retroviral Vector.* Sponsor: Enzo Therapeutics, Inc.

NIH/ORDA Receipt Date: 1-20-98. Not Selected for RAC Public Review: 3-26-98

9802-231 (Open) Gene Therapy/Phase I/II/Monogenic Disease/Chronic Granulomatous Disease/In Vitro/CD 34+ Autologous Peripheral Blood Cells/Retrovirus/p47phox/gp91phox/Intravenous

Malech, Harry L.; National Institutes of Health, Bethesda, Maryland; *Gene Therapy Approach for Chronic Granulomatous Disease.*

NIH/ORDA Receipt Date: 2-2-98. Not Selected for RAC Public Review: 2-20-98

9802-232 (Closed) Gene Therapy/Phase I/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Administration

Isner, Jeffrey M.; Tufts University School of Medicine, Boston, Massachusetts; *Gene Therapy for Myocardial Angiogenesis.*

NIH/ORDA Receipt Date: 2-3-98. Publicly Reviewed at the June 18, 1998 RAC meeting
Follow-up has been completed: 11-29-01

9802-233 (Closed) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral Injection

Dreicer, Robert; the University of Iowa Hospitals and Clinics, Iowa City, Iowa; Seigler, Hilliard; Duke University Medical Center, Durham, North Carolina; Rubin, Joseph; Mayo Clinic, Rochester, Minnesota; DeConti, Robert; H. Lee Moffitt Cancer Center, Tampa, Florida; Gonzalez, Rene; the University of Colorado Cancer Center, Denver Colorado; Macdonald, John S.; Saint Vincent's Hospital and Medical Center, New York, NY; Hutchins, Laura; University of Arkansas for Medical Sciences, Little Rock, Arkansas; Samlowski, Wolfram E.; the University of Utah Health Sciences Center, Salt Lake City, Utah; Bearden, James D.; Spartanburg Regional Medical Center, Spartanburg, South Carolina; Atkins, Michael B., Beth Israel Medical Center, Boston, Massachusetts; Schwarzenberger, Paul O., Louisiana State University Medical Center, New Orleans, Louisiana; Deisseroth, Albert, Yale University School of Medicine, New Haven, Connecticut; Blum, Ronald H., Beth Israel Medical, New York, New York; Lutzky, Jose, Mount Sinai Medical Center, Miami, Florida; and Wallach, Sabina R., Scripps Memorial Hospital, San Diego, La Jolla, and Encinitas, California; *Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 2-9-98. Not Selected for RAC Public Review: 8-28-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9802-234 (Closed) Gene Therapy/Phase III/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral Injection

Thompson, John A.; University of Washington, Seattle, Washington; Dreicer, Robert; the University of Iowa Hospitals and Clinics, Iowa City, Iowa; Seigler, Hilliard; Duke University Medical Center, Durham, North Carolina; Galanis, Evanthia; Mayo Clinic, Rochester, Minnesota; DeConti, Robert; H. Lee Moffitt Cancer Center, Tampa, Florida; Macdonald John S.; Saint Vincent's Hospital and Medical Center, New York, NY; Hutchins, Laura; University of Arkansas for Medical Sciences, Little Rock, Arkansas; Samlowski, Wolfram E.; the University of Utah Health Sciences Center, Salt Lake City, Utah; Bearden, James D.; Spartanburg Regional Medical Center, Spartanburg, South Carolina; Atkins, Michael B., Beth Israel Medical Center, Boston, Massachusetts; Gibbs, John and Oleksowicz, Leslie, Roswell Park Cancer Institute, Buffalo, New York; Schwarzenberger, Paul O., Louisiana State University Medical Center, New Orleans, Louisiana; Ernstoff, Marc, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; Campbell, Laura, Louisiana State University Medical Center, Shreveport, Louisiana; Levine, Edward, Wake Forest University Medical Center, Winston-Salem, North Carolina; Schuchter, Lynn M., University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania; Deisseroth, Albert, Yale University School of Medicine, New Haven, Connecticut; Paciucci, Paolo A., Mount Sinai Medical Center, New York, New York; Richart, John, Saint Louis University Health Sciences Center, St. Louis, Missouri; Meyskens Jr., Frank L., University of California, Irvine, Orange, California; Blum, Ronald H., Beth Israel Medical, New York, New York; Amatruda, Thomas, Virginia Piper Cancer Institute Abbott Northwestern Hospital, Minneapolis, Minnesota; Kuzel, Timothy, Northwestern Medical Faculty Foundation and Northwestern Memorial Hospital, Chicago, Illinois; Hawkins, Michael, Washington Cancer Institute, Washington, DC; Whitman, Eric D., The Melanoma Center of St. Louis, Saint Louis, Missouri; Cobb, Patrick, Billings Interhospital Oncology Project, Billings, Montana; Amin, Bipinkumar, Mid Dakota Clinic, Bismarck, North Dakota; Chowhan, Naveed, Cancer Care Center Incorporated, New Albany, Indiana; Lutzky, Jose, Mount Sinai Medical Center, Miami, Florida; Amatruda, Thomas, North Memorial Healthcare, Hubert H. Humphrey Cancer Center, Robbinsdale, Minnesota ;Patel, Ravi, Comprehensive Blood and Cancer Center, Bakersfield, California; Dobbs, Tracy W., Baptist Hospital of East Tennessee, Knoxville, Tennessee; Ahmed, Fakhiuddin, HemOnCare, P.C., Brooklyn, New York; Thant, Myo, Maryland Hematology/Oncology Associates, Baltimore, Maryland; Stark, James J., Maryview Medical Center, Portsmouth, Virginia; Arena, Francis, Arena Oncology Associates, Great Neck, New York; Brotherton, Timothy, Danville Hematology and Oncology, Inc. Danville Diagnostic Imaging Center, Danville, Virginia; Brouillard, Robert P., Scripps Memorial Hospital, La Jolla, Encinitas, and El Cajon, California; Polikoff, Jonathan A., Kaiser Permanente Medical Group, San Diego, California; Ritch, Paul S., Medical College of Wisconsin and Froedtert Memorial Lutheran Hospital, Milwaukee, Wisconsin; Bernstein, Joel I., Scripps Memorial Hospital, La Jolla, Encinitas, El Cajon, California; Richards, Jon, Lutheran General Hospital, Park Ridge, Illinois; and Giguere, Jeffrey, Hematology and Oncology Associates, Greenville, South Carolina; *A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 2-9-98. Not Selected for RAC Public Review: 7-20-98

9802-235 (Open) Gene Therapy/Phase I/Cancer/Brain Tumors/Glioblastoma/Vector-Directed Cell Lysis/In Vivo/Autologous Tumor Cells/Herpes Simplex Virus Type I/Tumor Lysis/Intratumoral Injection

Markert, James; University of Alabama, Birmingham, Alabama; and Medlock, Michael; Georgetown University Medical Center, Washington, D.C.; *A Dose Escalating Phase I Study of the Treatment of Malignant Glioma with G207, a Genetically Engineered HSV-1.* Sponsor: NeuroVir, Inc.

NIH/ORDA Receipt Date: 2-10-98. Publicly Reviewed at the June 18, 1998 RAC meeting

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9802-236 (Open) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/In Vivo/Autologous Tumor Cells/Adenovirus Type 5/Replication-competent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen/Intratumoral Injection

Simons, Jonathan W.; Johns Hopkins University School of Medicine, Baltimore, Maryland; *A Phase I Study of the Intraprostatic Injections of CN706, a Prostate-Specific Antigen Gene-Regulated Cytolytic Adenovirus, in Patients with Locally Recurrent Cancer Following Definitive Radiotherapy.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 2-13-98. Publicly Reviewed at the June 19, 1998 RAC meeting

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9802-237 (Closed) Gene Therapy/Phase I/Rheumatoid Arthritis/In Vivo/Autologous Synovial Cells/Naked Plasmid DNA/Herpes Simplex Virus Thymidine Kinase Gene/Ganciclovir/Intra-Articular Administration

Roessler, Blake J; The University of Michigan Medical Center, Ann Arbor, Michigan; *Molecular Synovectomy by In Vivo Gene Transfer: A Phase I Trial.*

NIH/ORDA Receipt Date: 2-13-98. Publicly Reviewed at the June 18, 1998 RAC meeting
Closed to new enrollment: 5-15-02; follow-up is continuing

9802-238 (Open) Gene Therapy/Phase I-II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Fibroblast Growth Factor (FGF) cDNA/Intracoronary Administration

Lee, Joon S.; University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; *Phase 1/2 Study of the Effects of Ascending Doses of Adenovirus Mediated Human FGF-4 Gene Transfer in Patients with Stable Exertional Angina.* Sponsor: Berlex Laboratories, Inc.

NIH/ORDA Receipt Date: 2-24-98. Publicly Reviewed at the June 18, 1998 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9802-239 (Closed) Gene Therapy/Phase I-II/Cancer/Hepatic Metastasis of Colorectal Carcinoma/Immunotherapy/In Vitro/Autologous CD4+ and CD8+ Lymphocytes/Retrovirus/CC49-Zeta T Cell Receptor/Hepatic Artery Infusion

Bergsland, Emily K.; University of California, San Francisco, San Francisco, California; *A Phase I/II Study of Hepatic Infusion of Autologous CC49-Zeta Gene-Modified T Cells in Patients with Hepatic Metastasis from Colorectal Cancer.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 2-25-98. Not Selected for RAC Public Review: 3-17-98

Notification from sponsor that trial is closed: 4-09-01

9803-240 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/ Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Rom, William N.; New York University School of Medicine, New York, New York; and Woo, Salvio L.C.; Mount Sinai School of Medicine, New York, New York; Phase *I Trial of Adenoviral Vector Delivery of the Herpes Simplex Thymidine Kinase Gene by Intratumoral Injection Followed by Intravenous Ganciclovir in Patients with Advanced Non-Small Cell Lung Cancer.*

NIH/ORDA Receipt Date: 3-3-98. Not Selected for RAC Public Review: 3-23-98

9803-241 (Closed) Gene Therapy/Phase I-II/Cancer/Chronic Myelogenous Leukemia/Multiple Myeloma/Non-Hodgkin's Lymphoma/Chronic Lymphocytic Leukemia/Adoptive Immunotherapy/In Vitro/Sibling Peripheral Blood Lymphocytes/Retrovirus/Herpes Simplex Virus Thymidine Kinase/Ganciclovir/Intravenous Infusion

Bensinger, William I.; University of Washington School of Medicine, Seattle, Washington; Parker, Pablo M.; City of Hope National Medical Center, Duarte, California; Henslee-Downey, Peggy J.; and Abhyankar, Sunil; Richland Memorial Hospital, University of South Carolina, Columbia, South Carolina; Giralt, Sergio; University of Texas, MD Anderson Cancer Center, Houston, Texas; Cornetta, Kenneth; Indiana University-Purdue University, Indianapolis, Indiana; and Carabasi, Matthew; The University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I/II Outpatient, Multicenter, Intrapatient, Multiple Dose Escalation Study of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Transduced Mononuclear Cells in Subjects with Persistent or Relapsed Chronic Myleogenous Leukemia, Chronic Lymphocytic Leukemia, Multiple Myeloma, and Non-Hodgkin's Lymphoma after HLA-Matched Sibling Allogeneic Stem Cell Transplant.* Sponsor: Chiron Corporation

NIH/ORDA Receipt Date: 3-27-98. Not Selected for RAC Public Review: 4-17-98
5-5-00: IND no longer active

9803-242 (Closed) Gene Therapy/Phase I/Cancer/Chronic Lymphocytic Leukemia/Immunotherapy/In Vitro/Autologous Leukemic Cells/Adenovirus/Serotype 5/CD 154 cDNA/Intravenous Infusion

Kipps, Thomas J.; University of California, San Diego, San Diego, California; *A Phase I Study of CD 154 Gene-Transduced Leukemia Cells in Patients with Chronic Lymphocytic Leukemia.*

NIH/ORDA Receipt Date: 3-30-98. Not Selected for RAC Public Review: 4-17-98

Notification from Immunogenex, now the sponsor of this trial, that study has been completed: 3-20-01

9804-243 (Open) Gene Therapy/Phase I/Other/Peripheral Arterial Disease/In Vivo/Ischemic Lower Limb/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Crystal, Ronald G.; Cornell University Medical College, New York, New York; Deitcher, Steven and Goldman, Corey, The Cleveland Clinic Foundation, Cleveland, Ohio; Rajagopalan, Sanjay, The University of Michigan, Ann Arbor, Michigan; Mohler III, Emile R., University of Pennsylvania Health System, Philadelphia, Pennsylvania; and Trachtenberg, Jeffrey, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; *Phase I Study of Direct Administration of a Replication Deficient Adenovirus vector ($Ad_{GV}VEGF121.10$) Containing the VEGF121 cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease.* Sponsor: Parke-Davis Pharmaceutical Research.

NIH/ORDA Receipt Date: 4-10-98. Not Selected for RAC Public Review: 4-30-98

9804-244 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Cationic Liposome Complex/Plasmid DNA/Interleukin-2 cDNA/Staphylococcus Enterotoxin B (SEB)/Intratumoral Injection

Walsh, Patrick; University of Colorado Health Sciences Center, Denver, Colorado; *A Phase I Study Using Direct Combination DNA Injections for the Immunotherapy of Metastatic Melanoma.*

NIH/ORDA Receipt Date: 4-10-98. Publicly Reviewed at the June 19, 1998 RAC meeting
Closed to enrollment, follow-up is continuing: 9-5-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9804-245 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) cDNA/Aerosol Administration

Moss, Richard; Stanford University School of Medicine, Palo Alto, California; Aitken, Moira, University of Washington Medical Center, Seattle, Washington; and Waltz, David, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Aerosolized tgAAVCF for the Treatment of Cystic Fibrosis Patients with Mild Lung Disease.* Sponsor: Targeted Genetics Corporation.

NIH/ORDA Receipt Date: 4-18-98. Not Selected for RAC Public Review: 12-3-98

9804-246 (Open) Gene Therapy/Phase II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Oncogene Regulation/HER-2/neu/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intratumoral Injection

Yoo, George H., Wayne State University School of Medicine, Detroit, Michigan; Villaret, Douglass B., University of Washington, Seattle, Washington; Gleich, Lyon, University of Cincinnati Medical Center, Cincinnati, Ohio; Hanna, Ehab, University of Arkansas Cancer Research Center, Little Rock, Arkansas; and Kenady, Daniel E., and Valentino, Joseph, University of Kentucky, Lexington, Kentucky; *A Multicenter Phase II Study of E1A Lipid Complex for the Intratumoral Treatment of Patients with Recurrent Head and Neck Squamous Cell Carcinoma.* Sponsor: Targeted Genetics Corporation.

NIH/ORDA Receipt Date: 4-18-98. Not Selected for RAC Public Review: 2-1-99

9804-247 (Open) Gene Therapy/Phase I/Monogenic Disease/Hemophilia A/In Vitro/Electroporation/Autologous Fibroblasts/Plasmid DNA/Factor VIII cDNA/Intraperitoneal Implantation

Roth, David A.; Beth Israel Deaconess Medical Center, Boston, Massachusetts; *A Phase I Safety Study of Autologous Transfected Human Fibroblasts Producing Human Factor VIII in Patients with Severe Hemophilia A.* Sponsor: Transkaryotic Therapies, Inc.

NIH/ORDA Receipt Date: 4-17-98. Publicly Reviewed at the June 19, 1998 RAC meeting

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9804-248 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Breast Cancer/Immunotherapy/In Vivo/Adenovirus/Serotype 5/B7.1 (CD80) cDNA/Intratumoral Injection

Schuchter, Lynn; University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *Phase I Trial of Therapeutic Cancer Vaccine Using Intratumoral Injections of B7-1 (H5.030CMVhB7) in Patients with Metastatic Melanoma or Metastatic Breast Cancer.*

NIH/ORDA Receipt Date: 4-23-98. Not Selected for RAC Public Review: 5-13-98

9804-249 (Open) Gene Therapy/Phase I/Cancer/Adenocarcinoma Expressing Carcinoembryonic Antigen (CEA)/In Vitro/Autologous T Lymphocytes/Retrovirus/anti-CEA-sFv-Zeta T Cell Receptor/Intravenous Infusion

Junghans, Richard Paul; Beth Israel Deaconess Medical Center, Boston, Massachusetts; *Phase I Study of T Cells Modified with Chimeric AntiCEA Immunoglobulin-T Cell Receptors (IgTCR) in Adenocarcinoma.*

NIH/ORDA Receipt Date: 4-28-98. Not Selected for RAC Public Review: 5-18-98

9804-250 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injections

Swisher, Steven; University of Texas M.D. Anderson Cancer Center/Texas Heart Institute, Houston, Texas; *An Efficacy Study of Adenoviral Vector Expressing Wildtype p53 (Ad5CMV-p53) Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer.* Sponsor: Aventis (formerly Gencell)

NIH/ORDA Receipt Date: 4-28-98. Not Selected for RAC Public Review: 5-18-98

9805-251 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/MUC -1/Interleukin-2/Intramuscular Injection

Figlin, Robert; University of California at Los Angeles, Los Angeles, California; *Phase I/II Trial of Antigen-Specific Immunotherapy in MUC-1 Positive Patients with Adenocarcinoma of the Prostate Using Vaccinia Virus-MUC1-IL2 (TG 1031).* Sponsor: Transgene, S.A.

NIH/ORDA Receipt Date: 5-1-98. Not Selected for RAC Public Review: 5-22-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9805-252 (Open) Gene Therapy/Phase I/Cancer/Colorectal/In Vitro/Allogeneic Tumor Cells and Fibroblasts/Lethally Irradiated/Plasmid DNA/Interleukin-2 cDNA/B7.1 (CD80)/Subcutaneous Injection

Sobol, Robert E.; Sidney Kimmel Cancer Center, San Diego, California; *A Phase I Study of Allogeneic Tumor Cells Genetically Modified to Express B7.1 (CD80) Mixed with Allogeneic Fibroblasts Genetically Modified to Secrete IL-2 in Patients with Colorectal Carcinoma.*

NIH/ORDA Receipt Date: 5-7-98. Not Selected for RAC Public Review: 5-27-98

9805-253 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD8+ T Cells/ Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous Infusion

Scadden, David T.; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts; Mitsuyasu, Ronald; University of California, Los Angeles, Los Angeles, California; and Deeks, Steven; University of California, San Francisco, San Francisco, California; *A Phase II Study of Autologous CD4-Zeta Gene-Modified T Cells in HIV Infected Patients with Undetectable Plasma Viremia on Highly Active Anti-Retroviral Drug Therapy* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 5-14-98. Not Selected for RAC Public Review: 6-3-98

Study closed to new accrual, follow-up is continuing: 7-13-01

9805-254 (Open) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Naked Plasmid/gp 100 Melanoma Antigen/Intradermal or Intramuscular Injection

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Immunization of Patients with Metastatic Melanoma Using DNA Encoding the GP100 Melanoma Antigen.* Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-4-98. Not Selected for RAC Public Review: 6-24-98

9806-255 (Closed) Gene Therapy/Phase I/Cancer/Ovarian/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intraperitoneal Administration

Muller, Carolyn Y.; University of Texas Southwestern Medical School, Dallas, Texas; *Phase I Trial of Intraperitoneal Adenoviral p53 Gene Therapy in Patients with Advanced Recurrent or Persistent Ovarian Cancer.* Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-2-98. Not Selected for RAC Public Review: 6-22-98
Closed to accrual: 4-15-02

9806-256 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intradermal and Subcutaneous Injections

Suzuki, Tsuneo; University of Kansas Medical Center, Kansas City, Kansas; *Autologous, Irradiated, Melanoma Cells Transduced Ex Vivo with an Adenovirus Vector (Adv/GM-CSF) Expressing Granulocyte-Macrophage Colony Stimulating Factor Gene.*

NIH/ORDA Receipt Date: 6-3-98. Not Selected for RAC Public Review: 6-23-98

9806-257 (Open) Gene Therapy/Phase I/Cancer/Breast/Colon/Head and Neck/Soft Tissue Sarcoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/ Adenovirus/Serotype 5/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intradermal and Subcutaneous Injections

Suzuki, Tsuneo; University of Kansas Medical Center, Kansas City, Kansas; *Autologous, Irradiated, Cancer Cells (Breast Cancer, Colon Cancer, Head and Neck Cancer, and Soft Tissue Sarcoma) Transduced Ex Vivo with an Adenovirus Vector (Adv/GM-CSF) Expressing Granulocyte-Macrophage Colony Stimulating Factor Gene.*

NIH/ORDA Receipt Date: 6-3-98. Not Selected for RAC Public Review: 6-23-98

9806-258 (Open) Gene Therapy/Phase I/ Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Crystal, Ronald G.; Cornell University Medical College, New York, New York; *Phase I Study of Direct Administration of a Replication Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease Via Minimally Invasive Surgery.* Sponsor: Parke-Davis Pharmaceutical Research.

NIH/ORDA Receipt Date: 6-8-98. Not Selected for RAC Public Review: 8-13-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9806-259 (Closed) Gene Therapy/Phase II/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1102/Interleukin-2 cDNA/Intratumoral Injection

Figlin, Robert; University of California at Los Angeles, Los Angeles, California; Thompson, John, A.; University of Washington, Seattle, Washington; Galanis, Evanthia; Mayo Clinic, Rochester, Minnesota; and Bukowski, Ronald, Cleveland Clinic Foundation, Cleveland, Ohio; *Phase II Study of Direct Gene Transfer of IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Renal Cell Carcinoma.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 6-15-98. Not Selected for RAC Public Review: 7-6-98

9806-260 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical-1005/HLA-B7/Beta 2-Microglobulin cDNA/Concurrent Interleukin-2 Injection/Direct Intratumoral Injection

Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; *Phase I Study of HLA-B7/β2M Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) by Direct Gene Transfer with Concurrent Low-Dose Subcutaneous IL-2 Protein Therapy as an Immunotherapeutic Regimen in Malignant Melanoma.*

NIH/ORDA Receipt Date: 6-26-98. Not Selected for RAC Public Review: 7-16-98

9806-261 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/Retrovirus/Transdominant Rev or Rev and Antisense Pol 1/Intravenous Infusion

Amado, Rafael G.; University of California at Los Angeles, Los Angeles, California; and Yuen, Alan R.; Stanford University Medical Center; Stanford, California; Scadden, David T., Massachusetts General Hospital, Boston, Massachusetts; Lill, Michael, Cedars-Sinai Medical Center, Los Angeles, California; and Carabasi, Matthew, University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I/II Study of the Safety and Feasibility of RevM10 or RevM10/Antisense Pol 1 Transduced Hematopoietic Stem Cells (HSC) in HIV-1 Related Non-Hodgkin's Lymphoma Patients Already Being Treated with High Dose Chemotherapy and Peripheral Blood Stem Cell Support.* Sponsor: Systemix, Inc.

NIH/ORDA Receipt Date: 6-30-98. Not Selected for RAC Public Review: 7-20-98

9807-262 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intraperitoneal Administration

Wolf, Judith K.; The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I Study of Ad-p53 (NSC#683550) for Patients with Platinum- and Paclitaxel-Resistant Epithelial Ovarian Cancer.*

NIH/ORDA Receipt Date: 7-24-98. Not Selected for RAC Public Review: 8-13-98

9808-263 (Open) Gene Therapy/Phase I/Cancer/Malignant Glioma/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Lang, Frederick F., Jr. and Yung, W. K. Alfred; The University of Texas MD Anderson Cancer Center, Houston, Texas; and Greenberg, Harry, University of Michigan, Ann Arbor, Michigan; *Phase I Trial of Adenovirus-Mediated Wild Type p53 Gene Therapy for Malignant Gliomas.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 8-13-98. Not Selected for RAC Public Review: 9-2-98

9808-264 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vivo/Vaccinia Virus/MUC-1/Interleukin-2/Intramuscular Injection

Gitlitz, Barbara J.; University of California Los Angeles, Los Angeles, California; *Phase I/II Trial of Antigen-Specific Immunotherapy in MUC-1 Positive Patients with Advanced Non-Small Cell Lung Cancer Using Vaccinia-Virus-MUC1-IL2 (TG1031).* Sponsor: Transgene, S.A.

NIH/ORDA Receipt Date: 8-27-98. Not Selected for RAC Public Review: 9-18-98

9809-265 (Open) Gene Therapy/Phase I/Cancer/Solid Tumors/Chemoprotection/In Vitro/Peripheral Blood CD34+ Cells/Retrovirus/O^6-Methylguanine DNA Methyltransferase cDNA/Intravenous Infusion

Gerson, Stanton L.; Case Western Reserve University, Cleveland, Ohio; *Mutant MGMT Gene Transfer Into Human Hematopoietic Progenitors to Protect Hematopoiesis During O^6-Benzylguanine (BG, NSC 637037) and BCNU Therapy of Advanced Solid Tumors.*

NIH/ORDA Receipt Date: 9-2-98. Not Selected for RAC Public Review: 9-23-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9809-266 (Open) Gene Therapy/Phase I-II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Human Interferon-alpha cDNA/Intratumoral Injection

McQuone, Shelly J.; The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *A Multi-Center, Open-Label, Multiple Administration, Rising Dose Study of the Safety, Tolerability, and Efficacy of IFN-alpha Gene Medicine in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: GeneMedicine, Inc.

NIH/ORDA Receipt Date: 9-22-98. Not Selected for RAC Public Review: 3-19-99

9810-267 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Morris, John C.; National Institutes of Health, Bethesda, Maryland; *A Phase I Study of Intralesional Administration of an Adenovirus Vector Expressing the HSV-1 Thymidine Kinase Gene (AdV.RSV-TK) in Combination with Escalating Doses of Ganciclovir in Patients with Cutaneous Metastatic Malignant Melanoma.*

NIH/ORDA Receipt Date: 10-6-98. Not Selected for RAC Public Review: 10-27-98

9810-268 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Irradiated/Adenovirus/Serotype 5/B7.1 (CD80) cDNA/Subcutaneous Injection

Antonia, Scott J.; University of South Florida, Tampa, Florida; *Treatment of Patients with Stage IV Renal Cell Carcinoma with B7-1 Gene-Modified Autologous Tumor Cells and Systemic IL-2.*

NIH/ORDA Receipt Date: 10-26-98. Not Selected for RAC Public Review: 11-30-98

Closed to new accrual: 3-29-01

9811-269 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/Type 5/MART-1 Melanoma Antigen/Intravenous or Intradermal Injection

Economou, James S., UCLA Medical Center, Los Angeles, California; *A Phase I Trial Testing MART-1 Genetic Immunization in Malignant Melanoma.*

NIH/ORDA Receipt Date: 11-17-98. Not Selected for RAC Public Review: 12-8-98

9811-270 (Closed) Gene Therapy/Phase II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/Beta2-Microglobulin cDNA/Direct Intratumoral Injection

Hanna, Ehab, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Wagman, Lawrence D., City of Hope National Medical Center, Duarte, California; Gluckman, Jack L., University of Cincinnati Medical Center, Cincinnati, Ohio; and Wolf, Gregory T., University of Michigan Medical Center, Ann Arbor, Michigan; *Phase II Study of the Safety, Efficacy, and Effect on Quality of Life of Allovectin-7 Immunotherapy for the Treatment of Recurrent or Persistent Squamous Cell Carcinoma of the Head and Neck.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 11-19-98. Not Selected for RAC Public Review: 2-5-99

9811-271 (Closed) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with Moderate-Risk Critical Limb Ischemia.* Sponsor: Vascular Genetics, Inc.

NIH/ORDA Receipt Date: 11-23-98. Not Selected for RAC Public Review: 12-14-98
Follow-up has been completed: 11-29-01

9811-272 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy/In Vivo/Vaccinia Virus/MUC-1/Intradermal Injection

Kufe, Donald W., Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Trial of Recombinant Vaccinia Virus that Expresses DF3/MUC1 in Patients with Metastatic Adenocarcinoma of the Breast.*

NIH/ORDA Receipt Date: 11-23-98. Not Selected for RAC Public Review: 12-24-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9812-273 (Open) Gene Therapy/Phase I-II/Infectious Diseases/Human Immunodeficiency Virus-1 (HIV-1)/In Vitro/Immunotherapy/Autologous CD8+ HIV-Specific T Cells/Retrovirus/Neomycin Phosphotransferase Gene/Intravenous Infusion

Riddell, Stanley R., Fred Hutchinson Cancer Research Center, Seattle, Washington; *The Safety and Antiviral Efficacy of Cellular Adoptive Immunotherapy with Autologous CD8+ HIV-Specific Cytotoxic T Cells Combined with Interleukin-2 for HIV Seropositive Individuals.*

NIH/ORDA Receipt Date: 12-3-98. Not Selected for RAC Public Review: 1-5-99

9812-274 (Closed) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Fibroblast Growth Factor (FGF) cDNA/Intramuscular Injection

Comerota, Anthony J., Temple University School of Medicine, Philadelphia, Pennsylvania; Laird, John R., Washington Hospital Center, Washington, D.C.; Sequeira, Rafael F., University of Miami, School of Medicine, Miami, Florida; Henry, Timothy, Hennepin County Medical Center, Minneapolis, Minnesota; and Chronos, Nicholas, Atlanta Cardiology Group, Atlanta, Georgia; *A Phase I, Multi-Center, Open Label, Safety and Tolerability Study of Increasing Single Dose of NV1FGF Administered by Intra-Muscular Injection in Patients with Severe Peripheral Artery Occlusive Disease.* Sponsor: Aventis (formerly Gencell).

NIH/ORDA Receipt Date: 12-17-98. Not Selected for RAC Public Review: 2-4-99

9812-275 (Open) Gene Therapy/Phase I/Cancer/Advanced Malignancies/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intravenous Injection

Eckhardt, S. Gail, Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, Texas; *A Pharmacokinetic, Safety and Tolerability Study of Intravenous INGN in Patients with Advanced Cancer.* Sponsor: Introgen Therapeutics, Inc.

NIH/ORDA Receipt Date: 12-18-98. Not Selected for RAC Public Review: 5-13-99

9812-276 (Open) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Valacyclovir/Intratumoral Injection

Gardner, Thomas A. and Chung, Leland W. K., University of Virginia Health, Charlottesville, Virginia; *Phase I Study of Ad-OC-TK Plus Valacyclovir for the Treatment of Metastatic or Recurrent Prostate Cancer.*

NIH/ORDA Receipt Date: 12-23-98. Not Selected for RAC Public Review: 1-14-99

9812-277 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/Retrovirus/Transdominant Rev/Antisense Pol 1/Intravenous Infusion

Amado, Rafael G., University of California, Los Angeles, Los Angeles, California; Carabasi, Matthew, University of Alabama at Birmingham, Birmingham, Alabama; Swindells, Susan, University of Nebraska Medical Center, Omaha, Nebraska; and Scadden, David T., Massachusetts General Hospital, Boston, Massachusetts; *A Phase I/II Study in HIV-1 Infected Patients Infused with CD34+Thy1+ Hematopoietic Stem Cells (HSC) from G-CSF Mobilized Peripheral Blood Retrovirally Transduced with RevM10 or RevM10/Antisense Pol1.* Sponsor: Systemix, Inc.

NIH/ORDA Receipt Date: 12-28-98. Not Selected for RAC Public Review: 1-19-99

9901-278 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Plasmid DNA/MART-1 Melanoma Antigen/Intramuscular Injection

Conry, Robert M., University of Alabama at Birmingham, Birmingham, Alabama; *Phase I Dose Escalation Trial of Polynucleotide Immunization with Plasmid DNA Encoding MART-1 (Melanoma Antigen Recognized by T Cells-1) in Patients with Resected Melanoma at Significant Risk for Relapse.*

NIH/ORDA Receipt Date: 1-4-99. Not Selected for RAC Public Review: 1-25-99

9901-279 (Open) Gene Therapy/Phase I/Monogenic Disease/Hemophilia B/In Vivo/Adeno-Associated Virus/Factor IX Gene/Intramuscular Injection

Manno, Catherine S., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *A Phase I Safety Study in Patients with Severe Hemophilia B (Factor IX Deficiency) Using Adeno-Associated Viral Vector to Deliver the Gene for Human Factor IX to Skeletal Muscle.* Sponsor: Avigen.

NIH/ORDA Receipt Date: 1-7-99. Publicly Reviewed at the March 12, 1999 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9901-280 (Open) Gene Therapy/Phase II-III/Cancer/Ovarian/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intraperitoneal Administration

Buller, Richard, The University of Iowa Hospitals and Clinics, Iowa City, Iowa; Carson, Linda F., University of Minnesota, Minneapolis, Minnesota; Weisberg, Tracey, Maine Center for Cancer Medicine, Scarborough, Maine; Christopherson, Wayne A., Mercy Hospital of Pittsburgh, Pittsburgh, Pennsylvania; Molpus, Kelly, University of Nebraska Medical Center, Omaha, Nebraska; Davidson, Susan A., University of Colorado Health Sciences Center, Denver, Colorado; Gutheil, John C., Sharp HealthCare, Sidney Kimmel Cancer Center, San Diego, California; Bloss, Jeffrey D., University of Missouri, Columbia, Missouri; Blum, Ronald, Beth Israel Medical Center, New York, New York; Puls, Larry E., Greenville Hospital System, Greenville, South Carolina; Teng, Nelson Nan-Hsiung, Stanford University School of Medicine, Stanford, California; Pergram, Mark D., University of California, Los Angeles, Los Angeles, California; Ueland, Federick, University of Kentucky Medical Center, Lexington, Kentucky; Rodriguez, Michael, University Hospitals of Cleveland, Cleveland, Ohio; Malfetano, John H., Albany Medical College, Albany, New York; Edwards, Robert P., University of Pittsburgh, Pittsburgh, Pennsylvania; Rader, Janet, Washington University, Saint Louis, Missouri; Benigno, Benedict B., Northside Hospital, Atlanta, Georgia; Lucci, Joseph T., University of Texas Medical Branch, Galveston, Texas; Delmore, James E., University of Kansas School of Medicine, Wesley Medical Center, Wichita, Kansas; Smith, Harriet O., University of New Mexico School of Medicine, Albuquerque, New Mexico; Bristow, Robert E., Johns Hopkins School of Medicine, Baltimore, Maryland; Abbas, Fouad, Sinai Hospital of Baltimore, Baltimore, Maryland; Fort, Giles, Woman's Hospital, Baton Rouge, Louisiana; Berchuck, Andrew, Duke University Medical Center; Coleman, Robert, University of Texas Southwestern Medical Center, Dallas, Texas; Rocereto, Thomas, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Camden, New Jersey; Hall, James, Carolinas Medical Center, Charlotte, North Carolina; Holloway, Robert, Walt Disney Memorial Cancer Institute, Orlando, Florida; Garcia, Agustin, University of Southern California, Norris Cancer Hospital, Los Angeles, California; Lentz, Samuel Wake Forest University School of Medicine, Winston-Salem, North Carolina; Swensen, Ron, Loma Linda University Cancer Institute, Loma Linda, California; Horowitz, Ira, Emory University School of Medicine, Atlanta, Georgia; Kline, Richard and Burroff, Janet, Alton Ochsner Medical Foundation, New Orleans, Louisiana; Scudder, Sidney, University of California, Davis, Sacramento, California; Noubisi, Boniface, University of Florida, Gainesville, Florida; and Celano, Paul, Greater Baltimore Medical Center, Baltimore, Maryland; *A Phase II/III Trial of Chemotherapy Alone Versus Chemotherapy Plus SCH 58500 in Newly Diagnosed Stage III Ovarian and Primary Peritoneal Cancer Patients with ≥0.5 cm and ≤2 cm Residual Disease Following Surgery.* Sponsor: Schering Corporation

NIH/ORDA Receipt Date: 1-12-99. Not Selected for RAC Public Review: 6-2-99

9901-281 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/Type 5/MART-1 Melanoma Antigen/gp 100 Melanoma Antigen/Subcutaneous Injection

Haluska, Frank, Harvard Medical School, Boston, Massachusetts and Nemunaitis, John J., US Oncology, Dallas, Texas; *Phase I/II Trial of the Safety, Immunogenicity, and Efficacy of Autologous Dendritic Cells Transduced with Adenoviruses Encoding the MART-1 and gp100 Melanoma Antigens Administered With or Without Low Dose Recombinant Interleukin-2 (rIL-2) in Patients with Stage IV Melanoma.* Sponsor: Genzyme Molecular Oncology.

NIH/ORDA Receipt Date: 1-12-99. Not Selected for RAC Public Review: 3-30-99

9901-282 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen/Intramuscular Injection

Eder, Joseph Paul, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase II Randomized Trial of Recombinant Fowlpox and Recombinant Vaccinia Virus Expressing PSA in Patients with Adenocarcinoma of the Prostate.* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP).

NIH/ORDA Receipt Date: 1-12-99. Not Selected for RAC Public Review: 1-24-00

9901-283 (Closed) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Small, Eric J., University of California, San Francisco, San Francisco, California; *Phase I/II Study of a Prime-Boost Schedule of Human GM-CSF Gene Transduced Irradiated Prostate Allogeneic Cancer Cell Vaccines (Allogeneic Prostate GVAX™) in Hormone-Naive Prostate Cancer Patients.* Sponsor: Cell Genesys

NIH/ORDA Receipt Date: 1-22-99. Not Selected for RAC Public Review: 2-11-99

Notification from sponsor that trial is closed: 4-09-01

9902-284 (Open) Gene Therapy/Phase I/Monogenic Disease/Hemophilia A/In Vivo/Retrovirus/Factor VIII cDNA/Intravenous Infusion

Ragni, Margret V., University of Pittsburgh, Pittsburgh, Pennsylvania; Lusher, Jeanne M., Children's Hospital of Michigan, Detroit, Michigan; Powell, Jerry S., University of California, Davis, Medical Center, Sacramento, California; White, Gilbert, University of North Carolina School of Medicine, Chapel Hill, North Carolina and Ewenstein, Bruce M., Brigham and Women's Hospital, Boston, Massachusetts; *Phase I Multi-Center, Single Treatment Dose Escalation Study of Factor VIII Vector [HFVIII(V)] for Treatment of Severe Hemophilia A.* Sponsor: Chiron Corporation

NIH/ORDA Receipt Date: 2-5-99. Publicly Reviewed at the September 3, 1999 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9902-285 (Open) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell Carcinoma/In Vivo/Cationic Liposome Complex with DC-Chol/Epidermal Growth Factor Receptor Antisense/Intratumoral Injection

Grandis, Jennifer Rubin, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; *A Phase I Trial of Intratumoral Antisense EGFR DNA and DC-Chol Liposomes in Advanced Oral Squamous Cell Carcinoma.*

NIH/ORDA Receipt Date: 2-12-99. Not Selected for RAC Public Review: 3-5-99

9902-286 (Open) Gene Therapy/Phase I/Cancer/Lung, Head and Neck/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/Beta 2-Microglobulin cDNA/Concurrent Interleukin-2 Injection/Direct Intratumoral Injection

Stopeck, Alison, Arizona Cancer Center, University of Arizona, Tucson, Arizona; *Phase I Study of HLA-B7/beta2M Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) by Direct Gene Transfer with Concurrent Low-Dose Subcutaneous IL-2 Protein Therapy as an Immunotherapeutic Regimen in Lung and Head and Neck Cancers.* Sponsor: Vical Inc.

NIH/ORDA Receipt Date: 2-16-99. Not Selected for RAC Public Review: 3-8-99

9902-287 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Bronchoalveolar Lavage

Schiller, Joan, University of Wisconsin, Madison, Wisconsin; and Carbone, David, P., Vanderbilt University Medical Center, Nashville, Tennessee; *Phase I Pilot Trial of Adenovirus p53 in Bronchioloalveolar Cell Lung Carcinoma (BAC) Administered by Bronchoalveolar Lavage.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 2-16-99. Not Selected for RAC Public Review: 3-25-99

9902-288 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection (Endobronchial or Percutaneous)

Schiller, Joan, University of Wisconsin, Madison, Wisconsin; *Phase I Pilot Trial of Adenovirus p53 and Radiotherapy on Non-Small Cell Lung Cancer.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 2-18-99. Not Selected for RAC Public Review: 6-24-99

9902-289 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Nasal Epithelial Cells/Cationic Liposome Complex/Alpha-1 Antitrypsin cDNA/Intranasal Administration

Brigham, Kenneth L., Vanderbilt University School of Medicine, Nashville, Tennessee; *Expression of an Exogenously Delivered Human Alpha-1 Antitrypsin Gene in Nasal Epithelium of Patients with Cystic Fibrosis.*

NIH/ORDA Receipt Date: 2-19-99. Not Selected for RAC Public Review: 4-2-99

9902-290 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Particle Mediated Gene Transfer (Accel®)/Plasmid DNA/gp 100 cDNA/Granulocyte-Macrophage Colony Stimulating Factor cDNA

Albertini, Mark R., University of Wisconsin, Madison, Wisconsin; *Phase I Trial of Immunization Using Particle-Mediated Transfer of Genes for GP-100 and GM-CSF into Uninvolved Skin of Patients with Melanoma.*

NIH/ORDA Receipt Date: 2-22-99. Not Selected for RAC Public Review: 3-15-99
3-29-00: Closed to accrual and treatment; follow-up will continue

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9902-291 (Open) Gene Therapy/Phase I/Monogenic Disease/Fanconi Anemia/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Fanconi Anemia Complementation Group A cDNA/Intravenous

Walsh, Christopher E., The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; *Retroviral-Mediated Gene Transfer of the Fanconi Anemia Group A Gene into Hematopoietic Progenitor Cells of Group A Patients.*

NIH/ORDA Receipt Date: 2-22-99. Not Selected for RAC Public Review: 3-15-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9902-292 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/gp 100 Melanoma Antigen/Intramuscular or Intravenous Injection

Rosenberg, Steven A., National Institutes of Health, Bethesda, Maryland; *Immunization of Patients with Metastatic Melanoma Using a Recombinant Fowlpox Virus Encoding a GP 100 Peptide Preceded by an Endoplasmic Reticulum Insertion Signal Sequence.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 2-24-99. Not Selected for RAC Public Review: 3-22-99

9902-293 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen/Intramuscular or Intradermal Injection

Kaufman, Howard, Albert Einstein College of Medicine, Bronx, New York; *Phase II Randomized Study of Vaccine Treatment of Advanced Prostate Cancer.* Sponsor: Eastern Cooperative Oncology Group

NIH/ORDA Receipt Date: 2-24-99. Not Selected for RAC Public Review: 8-13-99

9902-294 (Closed) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Administration

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts, Henry, Timothy D., Hennepin County Medical Center, Minneapolis, Minnesota and Schatz, Richard A., Scripps Clinic, La Jolla, California; *A Multicenter, Open-Label, Dose-Escalating Study of Intramyocardial Vascular Endothelial Growth Factor 2 (VEGF-2) Gene Therapy in Refractory Patients with Stable Exertional Angina Who Are Not Candidates for Revascularization Procedures.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 2-26-99. Not Selected for RAC Public Review: 6-11-99

9903-295 (Withdrawn from RAC Review) Gene Therapy/Phase I/Monogenic Disease/Gyrate Atrophy/In Vitro/Autologous Keratinocytes/Retrovirus/Ornithine Aminotransferase (OAT) cDNA/Skin Patch Administration

Nussenblatt, Robert B., National Institutes of Health, Bethesda, Maryland; *Phase I Study in the Safety and Efficacy of Transduced Keratinocytes for Possible Treatment of Gyrate Atrophy.*

NIH/ORDA Receipt Date: 3-4-99. Withdrawn from RAC review: 9-18-00

9903-296 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Human Gamma Interferon cDNA/Intratumoral Injection

Rosenblatt, Joseph D., University of Rochester Medical Center, Rochester, New York; *Phase I Trial of Immunotherapy with Adenovirus-Interferon-Gamma (TG1041) in Patients with Malignant Melanoma.* Sponsor: Transgene, Inc.

NIH/ORDA Receipt Date: 3-10-99. Not Selected for RAC Public Review: 3-30-99

Closed by sponsor to further enrollment: 06-29-01

9903-297 (Open) Gene Marking/Autoimmune Disease/Multiple Sclerosis/In Vitro/CD34+ Autologous Peripheral Blood/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Infusion

Krance, Robert, Baylor College of Medicine, Houston, Texas; *Intensive Immunosuppression Followed by Rescue with CD34 Selected, T Cell Depleted, Leukopheresis Products in Patients with Multiple Sclerosis.*

NIH/ORDA Receipt Date: 3-24-99. Not Selected for RAC Public Review: 4-21-99

9903-298 (Open) Gene Therapy/Phase II/Cancer/Ovarian/Pro-Drug/In Vivo/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraperitoneal/Catheter

Link, Charles J., and Morrman, Donald, Human Gene Therapy Research Institute, Des Moines, Iowa; *A Phase II Trial of In Vivo Gene Therapy with the Herpes Simplex Thymidine Kinase for the Treatment of Ovarian Cancer.*

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9903-299 (Open) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts, Baumgartner, Iris, Bern University, Bern Switzerland and Olin, Jeffrey Wayne, Cleveland Clinic Foundation, Cleveland, Ohio; *A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with Moderate-Risk Critical Limb Ischemia.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99

9903-300 (Closed) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with High-Risk Critical Limb Ischemia.*

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99
Follow-up has been completed: 11-29-01

9903-301 (Open) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts, Baumgartner, Iris, Bern University, Bern Switzerland and Olin, Jeffrey Wayne, Cleveland Clinic Foundation, Cleveland, Ohio; *A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with High-Risk Critical Limb Ischemia.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99

9903-302 (Closed) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Open-Label, Rescue-Therapy Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with Moderate-Risk or High-Risk Critical Limb Ischemia.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99
Follow-up is complete: 11-29-01

9903-303 (Closed) Gene Marking/Cancer/Neuroblastoma/Sarcoma/Retinoblastoma/In Vitro/CD34+ Autologous Peripheral Blood or Bone Marrow/Dihydrofolate Reductase cDNA/Intravenous Infusion

Cunningham, John M., St. Jude Children's Research Hospital, Memphis, Tennessee; *Tumor Purging of Autologous Stem Cell Grafts in Children with High-Risk Solid Tumors: Transplantation of Retrovirally Marked Stem Cell Grafts Purified by CD34+ Antibody Selection and High-Speed Cell Sorting.*

NIH/ORDA Receipt Date: 3-29-99. Not Selected for RAC Public Review: 5-18-99
Closed: 11-4-02

9904-304 (Open) Gene Therapy/Phase I/Cancer/Retinoblastoma/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection (Intraocular Tumor)

Hurwitz, Richard L., Baylor College of Medicine, Houston, Texas; *Pediatric Phase I Study of AdV/RSV-TK Followed by Ganciclovir for Retinoblastoma*

NIH/ORDA Receipt Date: 4-1-99. Publicly Reviewed at the June 14, 1999 RAC meeting

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9904-305 (Open) Gene Therapy/Phase I/Cancer/Breast/Tumor Suppressor Gene/In Vitro/Autologous CD34+ Cells/Adenovirus/Serotype 5/p53 cDNA/Intravenous Infusion

Baynes, Roy D., Karmanos Cancer Institute, Wayne State University, Detroit, Michigan; *A Phase I Study of Infused Mobilized, Autologous Peripheral Blood Progenitor Cells, Which Have Been Incubated with a Recombinant Adenovirus-Wild-Type p53 Construct (SCH 58500) to Purge Any Contaminating Breast Cancer Cells, As Stem Cell Support After High-Dose Chemotherapy in Patients with Breast Cancer Metastatic to Bone and Bone Marrow.*

NIH/ORDA Receipt Date: 4-5-99. Not Selected for RAC Public Review: 5-3-99

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9904-306 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Prostate Specific Antigen/Intravenous

Vieweg, Johannes, Duke University Medical Center, Durham North Carolina; *Safety and Feasibility Study of Active Immunotherapy in Patients with Hormone Refractory Prostate Cancer Using Autologous Dendritic Cells Pulsed with RNA Encoding Prostate Specific Antigen, PSA*

NIH/ORDA Receipt Date: 4-6-99. Not Selected for RAC Public Review: 4-26-99

9904-307 (Closed) Gene Therapy/Phase I/Cancer/Cervical/Immunotherapy/In Vivo/Vaccinia Virus/Human Papilloma Virus E6 and E7/Interleukin-2/Intramuscular Injection

Kaufman, Raymond H., Baylor College of Medicine, Houston, Texas; *Phase I Trial of Immunotherapy with MVA-HPV-IL2 (TG4001) in Women with Cervical Intraepithelial Neoplasia (CIN) Grade 3.* Sponsor: Transgene, Inc.

NIH/ORDA Receipt Date: 4-8-99. Not Selected for RAC Public Review: 4-26-99

9904-308 (Open) Gene Therapy/Phase I/Cancer/Leukemia/Adoptive Immunotherapy/In Vitro/Donor CD8+ Lymphocytes/Retrovirus/Hygromycin Phosphotransferase-Herpes Simplex Thymidine Kinase Fusion Gene/Intravenous Infusion

Warren, Edus, Fred Hutchinson Cancer Research Center, Seattle, Washington; *Phase I Study of Adoptive Immunotherapy with Gene-Modified and Unmodified CD8+ Minor Histocompatibility (H) Antigen-Specific CTL Clones for Patients with Relapse of AML or ALL After Allogeneic Hematopoietic Stem Cell Transplant.*

NIH/ORDA Receipt Date: 4-13-99. Not Selected for RAC Public Review: 5-3-99

9904-309 (Closed) Gene Therapy/Phase I/Cancer/Cervical Cancer/Immunotherapy/In Vivo/Vaccinia Virus/Human Papilloma Virus E6 and E7/Interleukin-2/Intramuscular Injection

Goff, Barbara A., University of Washington School of Medicine, Seattle, Washington; *Phase I Trial of Immunotherapy with MVA-HPV-IL2 (TG4001) in Women with Advanced Cervical Carcinoma.* Sponsor: Transgene, Inc.

NIH/ORDA Receipt Date: 4-22-99. Not Selected for RAC Public Review: 5-12-99

9904-310 (Open) Gene Marking/Osteodysplasia/In Vitro/Stromal Cells for Donor Bone Marrow/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Infusion

Horwitz, Edwin M., St. Jude Children's Research Hospital, Memphis, Tennessee; *Stromal Therapy of Osteodysplasia After Allogeneic Bone Marrow Transplantation: A Phase I Study.*

NIH/ORDA Receipt Date: 4-22-99. Not Selected for RAC Public Review: 5-12-99

9904-311 (Open) Gene Marking/Cancer/Neuroblastoma/In Vitro/Autologous Cytotoxic T-Lymphocytes from Peripheral Blood/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Infusion

Nuchtern, Jed, Baylor College of Medicine, Houston, Texas; *Administration of Neomycin Resistance Gene Marked Neuroblastoma Specific Cytotoxic T-Lymphocytes to Patients with Relapsed/Resistant Neuroblastoma.*

NIH/ORDA Receipt Date: 4-30-99. Not Selected for RAC Public Review: 5-20-99

9905-312 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1102/Leuvectin/Interleukin-2 cDNA/Intratumoral Injection

Belldegrun, Arie, University of California, Los Angeles, Los Angeles, California; Klein, Eric, Cleveland Clinic Foundation, Cleveland, Ohio; Corman, John, VA Puget Sound Health Care System, Seattle, Washington; and Moul, Judd, Walter Reed Army Medical Center, Washington, DC; *Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 5-7-99. Not Selected for RAC Public Review: 5-27-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9905-313 (Open) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/Vaccinia Virus/Tyrosinase cDNA/Intramuscular Injection

Topalian, Suzanne L., National Institutes of Health, Bethesda, Maryland; *Immunization of Patients with Metastatic Melanoma Using Recombinant Fowlpox and Vaccinia Viruses Encoding the Tyrosinase Antigen.*

NIH/ORDA Receipt Date: 5-11-99. Not Selected for RAC Public Review: 6-1-99

9905-314 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Vaccinia Virus/B7.1 (CD80)/Intratumoral Injection

Kaufman, Howard L., Columbia University, New York, New York; *A Phase I Trial of Intralesional RV-B7.1 Vaccine in the Treatment of Malignant Melanoma.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 5-12-99. Not Selected for RAC Public Review: 7-23-99
Closed: 5-15-02; follow-up is continuing

9905-315 (Closed) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Small, Eric J., University of California, San Francisco, San Francisco, California and Smith, David C., University of Michigan, Ann Arbor, Michigan; *A Phase I/II Study of a Prime-Boost Schedule of Human GM-CSF Gene Transduced Irradiated Prostate Allogeneic Cancer Vaccine (Allogeneic Prostate GVAX™) in Hormone-Refractory Prostate Cancer (G9803)* . Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 5-14-99. Not Selected for RAC Public Review: 6-4-99

Notification from sponsor that trial is closed: 4-09-01

9905-316 (Closed) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Percutaneous Cardiac Catheterization

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *Multicenter, Randomized, Single-Blind, Placebo-Controlled, Dose-Escalating Study of Intramyocardial Vascular Endothelial Growth Factor 2 (VEGF2) Gene Therapy Administered Using Percutaneous Cardiac Catheterization in Patients with Refractory and Stable Exertional Angina Who Are Not Candidates for Revascularization Procedures.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 5-21-99. Not Selected for RAC Public Review: 8-30-99
Follow-up is complete: 11-29-01

9905-317 (Open) Gene Therapy/Phase I/Monogenic Disease/Muscular Dystrophy/In Vivo/Adeno-Associated Virus/ α, β, γ, Δ-Sarcoglycan cDNA/Intramuscular Injection

Mendell, Jerry, Ohio State University, Columbus, Ohio; *Phase I Clinical Trial Utilizing Gene Therapy for Limb Girdle Muscular Dystrophy: α, β, γ or Δ-Sarcoglycan Gene Delivered with Intramuscular Instillations of Adeno-Associated Vectors.*

NIH/ORDA Receipt Date: 5-26-99. Publicly Reviewed at the September 2, 1999 RAC meeting

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9905-318 (Closed) Gene Therapy/Phase II/Cancer/Colon/Hepatic Metastasis/Tumor Suppressor Gene/n Vivo/Adenovirus/Serotype 5/p53 cDNA/Intrahepatic/Hepatic Artery/Bolus Infusion

Venook, Alan P. and Warren, Robert S. Warren, University of California, San Francisco, San Francisco, California; Lenz, Heinz-Josef, University of Southern California, Los Angeles, California; Ravikumar, Thanjavur S., Montefiore Medical Center, Bronx, New York; Kardinal, Carl, Alton Ochsner Medical Foundation, New Orleans, Louisiana; Roh, Mark S., Allegheny General Hospital, Pittsburgh, Pennsylvania; Kemeny, Margaret, Stony Brook University Hospital, Stony Brook, New York; Gold, Philip J., University of Washington, Seattle, Washington; Staley III, Charles, Emory University School of Medicine, Atlanta, Georgia; McMasters, Kelly M., University of Louisville, Louisville, Kentucky; Elias, Laurence, University of New Mexico School of Medicine, Albuquerque, New Mexico; and Amado, Rafael G., University of California, Los Angeles, Los Angeles, California; *A Phase II Study of SCH 58500 in Combination with Chemotherapy Alone in Patients with Colorectal Cancer Metastatic to the Liver.* Sponsor: Schering Corporation.

NIH/ORDA Receipt Date: 5-26-99. Not Selected for RAC Public Review: 6-16-99

Notification from sponsor that study is closed to new enrollment at all sites: 3-29-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9905-319 (Open) Gene Therapy/Phase I/Cancer/Acute Leukemia/Immunotherapy/In Vitro/Autologous Bone Marrow Fibroblasts/Lethally Irradiated/Adenovirus/Serotype 5/Interleukin-2 cDNA/CD40 Ligand cDNA/subcutaneous Injection

Brenner, Malcolm, Baylor College of Medicine, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas; *Treatment of High Risk Acute Leukemia with CD40 Ligand and IL-2 Gene Modified Autologous Bone Marrow Fibroblasts and Tumor Cells.*

NIH/ORDA Receipt Date: 5-26-99. Not Selected for RAC Public Review: 6-16-99

9905-320 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Carcinoembryonic Antigen/Intravenous

Lyerly, H. Kim, Duke University Medical Center, Durham, North Carolina; *Pilot Study of CEA RNA-Loaded, FLT3 Ligand-Mobilized Peripheral Blood Antigen Presenting Cells for Patients with Metastatic Malignancies Expressing CEA.*

NIH/ORDA Receipt Date: 5-26-99. Not Selected for RAC Public Review: 9-23-99

9906-321 (Completed) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/Replication-Competent Virus/Pro-Drug/In Vivo/Adenovirus/E. coli Cytosine Deaminase cDNA/5-Fluorocytosine/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Kim, Jae Ho, Henry Ford Health System, Detroit, Michigan; *A Phase I Study of E1B-Attenuated Replication Competent Adenovirus Vector-Mediated Intratumoral Administration of the E. coli Cytosine Deaminase/HSV-1 Thymidine Kinase Fusion Gene in Conjunction with Two Prodrugs, 5-Fluorocytosine and Ganciclovir for Patients with Local Recurrence of Prostate Cancer after Radiation Therapy.*

NIH/ORDA Receipt Date: 6-9-99. Not Selected for RAC Public Review: 6-29-99

Study is completed: 7-3-02

9906-322 (Closed) Gene Therapy/Phase I/Alzheimer's Disease/In Vitro/Autologous Fibroblasts/Retrovirus/Nerve Growth Factor cDNA/Intracerebral Implantation

Tuszynski, Mark H., University of California, San Diego, La Jolla, California; *A Phase I Study of NGF Ex Vivo Gene Therapy for Alzheimer's Disease*

NIH/ORDA Receipt Date: 6-15-99. Publicly Reviewed at the December 1999 RAC meeting.

Closed to enrollment: 6-18-02

9906-323 (Open) Gene Therapy/Phase II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Cationic Liposome Complex/DOTMA-Cholesterol/Interleukin-2 cDNA/Intratumoral Injection

Zarrabi, M. H., Veterans Affairs Medical Center, Northport, New York; Biel, Merrill A., Ear, Nose & Throat SpecialtyCare of Minnesota, P.A., Minneapolis, Minnesota; Krasnow, Steven, Veterans Affairs Medical Center, Washington, D.C.; Cornett, Patricia, University of California, San Francisco/Veterans Affairs Medical Center, San Francisco, California; Robbins, K. Thomas, University of Tennessee, Memphis, Tennessee; O'Malley, Bert W., University of Maryland School of Medicine, Baltimore, Maryland; Kabbinavar, Fairooz, University of California, Los Angeles, Los Angeles, California; McCaffery, Thomas, University of South Florida, Tampa, Florida; and Cordero, Joehassin, Texas Tech University, Lubbock, Texas; *A Multi-Center, Open-Label, Study of the Safety and Efficacy of Multiple Intratumoral Injections of hIl-2 Plasmid (1.8 mg) Formulated with DOTMA/Cholesterol [Ratio 1:0.5 (-/+)] Liposomes in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck.* Sponsor: Valentis, Inc.

NIH/ORDA Receipt Date: 6-17-99. Not Selected for RAC Public Review: 7-8-99

9906-324 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Pro-Drug/Valacyclovir/In Vivo/Adenovirus/Herpes Simplex Thymidine Kinase cDNA/Intratumoral Injection

Butler, E. Brian and Aguilar-Cordova, Estuardo, Baylor College of Medicine, Houston, Texas; *Phase I-II Study Evaluating HSV-tk + Valacyclovir Gene Therapy in Combination with Radiotherapy for Prostate Cancer.*

NIH/ORDA Receipt Date: 6-22-99. Not Selected for RAC Public Review: 7-13-99

9906-325 (Open) Gene Therapy/Phase I/Cancer/Malignant Glioma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Human Interferon-Beta cDNA/Stereotactic Injection

Eck, Stephen L., University of Pennsylvania, Philadelphia, Pennsylvania; *Treatment of Recurrent or Progressive Malignant Glioma with a Recombinant Adenovirus Expressing Human Interferon-Beta (H5.010CMVhIFN-β): A Phase I Trial.*

NIH/ORDA Receipt Date: 6-30-99. Not Selected for RAC Public Review: 7-21-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9906-326 (Open) Gene Therapy/Phase I/Cancer/Skin Metastasis/Immunotherapy/In Vivo/Plasmid DNA/Interleukin-12 cDNA/Intratumoral Injection

Mahvi, David M., University of Wisconsin, Madison, Wisconsin; *Treatment of Spontaneous Tumor Metastases with IL-12 DNA: A Phase IB Trial.*

NIH/ORDA Receipt Date: 6-30-99. Not Selected for RAC Public Review: 7-21-99

9907-327 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Muscle Cells/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Intramuscular Injection

Losordo, Douglas W., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; Chronos, Nicholas, Atlanta Cardiology Group, Saint Joseph's Hospital, Atlanta, Georgia; Deitcher, Steven, Cleveland Clinic Foundation, Cleveland, Ohio; Rajagopalan, Sanjay, University of Michigan; and Laird, John, Washington Hospital Center, Washington, DC; *A Phase I Double-Blind, Placebo Controlled, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization.* Sponsor: Genzyme Corporation.

NIH/ORDA Receipt Date: 7-6-99. Not Selected for RAC Public Review: 10-5-99

9907-328 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Muscle Cells/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Intramuscular Injection

Losordo, Douglas W., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; Chronos, Nicholas, Atlanta Cardiology Group, Saint Joseph's Hospital, Atlanta, Georgia; Deitcher, Steven, Cleveland Clinic Foundation, Cleveland, Ohio; Rajagopalan, Sanjay, University of Michigan; and Laird, John, Washington Hospital Center, Washington, DC; *A Phase I, Open-Label, Multi-Center Extension Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization.* Sponsor: Genzyme Corporation.

NIH/ORDA Receipt Date: 7-6-99. Not Selected for RAC Public Review: 10-5-99

9907-329 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Muscle Cells/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Intramuscular Injection

Losordo, Douglas W., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; Chronos, Nicholas, Atlanta Cardiology Group, Saint Joseph's Hospital, Atlanta, Georgia; Deitcher, Steven, Cleveland Clinic Foundation, Cleveland, Ohio; Rajagopalan, Sanjay, University of Michigan; and Laird, John, Washington Hospital Center, Washington, DC; *A Phase I, Open-Label, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization.* Sponsor: Genzyme Corporation.

NIH/ORDA Receipt Date: 7-6-99. Not Selected for RAC Public Review: 10-5-99

9907-330 (Closed) Gene Therapy/Phase I/Cancer/CD20+ Lymphoma/In Vitro/Autologous T Lymphocytes/Plasmid DNA/Electroporation/CD20-Specific scFvFc-Zeta T Cell Receptor/Intravenous Infusion

Jensen, Michael, City of Hope National Medical Center, Duarte, California; *Pilot Phase I Study to Evaluate the Safety of Cellular Immunotherapy Using Genetically Modified Autologous CD20-Specific CD8+ T Cell Clones for Patients with Recurrent/Refractory CD20+ Lymphoma Undergoing Autologous Peripheral Blood Stem Cell Transplantation.*

NIH/ORDA Receipt Date: 7-8-99. Not Selected for RAC Public Review: 7-28-99

9907-331 (Withdrawn-replaced by protocol # 0004-393) Gene Therapy/Phase II/Cancer/Non-Small Cell Lung Cancer/Antisense/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Plasmid DNA/Electroporation/TGF-β/Subcutaneous Injection

Gutheil, John C. and Fakhrai, Habib, Sharp HealthCare, Sidney Kimmel Cancer Center, San Diego, California; *Phase II Study of Antisense TGF-β +/- IL-2 Gene Transfected Allogeneic Tumor Cells as a Vaccine in Patients with Stage IIIB and IV Non-Small Cell Lung Cancer.* Sponsor: NovaRx Corporation.

NIH/ORDA Receipt Date: 7-8-99.

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9907-332 (Open) Gene Therapy/Phase I-II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Interleukin-12 cDNA/Intratumoral Injection

Colevas, Alexander Dimitrios, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Multi-Center, Open-Label, Multiple Administration, Rising Dose Study of the Safety, Tolerability, and Efficacy of IL-12 Gene Medicine in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Valentis, Inc.

NIH/ORDA Receipt Date: 7-16-99. Not Selected for RAC Public Review: 8-5-99

9908-333 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD34+ Hematopoietic Stem Cells/Retrovirus/Transdominant Rev/Antisense Pol 1/Intravenous Infusion

Swindells, Susan, University of Nebraska Medical Center, Omaha, Nebraska; Scadden, David, Massachusetts General Hospital, Boston, Massachusetts; Holodniy, Mark, Veterans Affairs Palo Alto Health Care System, Palo Alto, California; and MacGregor, Rob Roy, University of Pennsylvania Hospitals, Philadelphia, Pennsylvania; *A Multicenter Evaluation of the Safety and Efficacy of Hematopoietic Stem Cells Transduced with RevM10polAS (RevM10polAS HSCIP) as Therapy for HIV-1 Infected Persons.* Sponsor: Systemix, Inc.

NIH/ORDA Receipt Date: 8-16-99. Not Selected for RAC Public Review: 9-3-99

9908-334 (Under Review) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine cDNA/Ganciclovir/Intraperitoneal Injection

Alvarez, Ronald D., Barnes, Mack N., and Curiel, David T. , University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Study of FGF2-Fab' Modified Adenovirus Vector Mediated Intraperitoneal Delivery of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Gene and Intravenous Ganciclovir in Previously Treated Ovarian and Extraovarian Patients.*

NIH/ORDA Receipt Date: 8-17-99. Review at a RAC meeting pending; investigators have requested postponement of public review.

9908-335 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Ovarian/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) cDNA/Subcutaneous or Intradermal Injection

Dranoff, Glenn, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Study of Vaccination with Lethally Irradiated, Autologous Ovarian Carcinoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor*

NIH/ORDA Receipt Date: 8-18-99. Not Selected for RAC Public Review: 9-8-99

9908-336 (Open) Gene Marking/Leukemia/In Vitro/CD 34+ Autologous Cord Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Croop, James and Cornetta, Kenneth., Indiana University School of Medicine; *Post-Transplant Infusion of Fibronectin-Assisted, Retroviral-Mediated Gene-Marked and Ex Vivo Expanded CD34+ Placental and Umbilical Cord Blood Cells*

NIH/ORDA Receipt Date: 8-19-99. Not Selected for RAC Public Review: 9-9-99

9908-337 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Monogenic Disease/Severe Combined Immune Deficiency due to adenosine Deaminase Deficiency/In Vitro/Autologous CD34+ Cells from Cord Blood or Bone Marrow/Retrovirus/Adenosine Deaminase cDNA/Intravenous Infusion

Kohn, Donald B., Childrens Hospital Los Angeles, University of Southern California, Los Angeles, California; and Brochstein, Joel, Hackensack University Medical Center, Hackensack, New Jersey; *Transduction of CD34+ Cells from the Umbilical Cord Blood of Infants or the Bone Marrow of Children with Adenosine Deaminase (ADA)-Deficient Severe Combined Immunodeficiency (SCID)*

NIH/ORDA Receipt Date: 8-26-99. Publicly Reviewed at the March 2000 RAC meeting

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9909-338 (Open) Gene Therapy/Phase I/Cancer/Prostate/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p 16 cDNA/Intratumoral Injection

Gingrich, Jeffrey R., University of Tennessee, Memphis, Tennessee; *A Tolerance and Efficacy Study of Neoadjuvant Intraprostatic GTx-001 Followed by Radical Prostatectomy in Patients with Locally Advanced Prostate Cancer.* Sponsor: Genotherapeutics, Inc.

NIH/ORDA Receipt Date: 9-2-99. Not Selected for RAC Public Review: 9-29-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9909-339 (Open) Gene Therapy/Phase I-II/Cancer/Ovarian/Tumor Suppressor Gene/In Vivo/Retrovirus/BRCA1 Gene/Intraperitoneal Administration

Holt, Jeffrey T., Vanderbilt University, Nashville, Tennessee, and Tait, David L., East Carolina University, Greenville, North Carolina; *Ovarian Cancer Gene Therapy with BRCA1.*

NIH/ORDA Receipt Date: 9-13-99. Not Selected for RAC Public Review: 10-1-99

9909-340 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD34+ Hematopoietic Stem Cells/Retrovirus/Transdominant Rev/Antisense Pol 1/Intravenous Infusion

Carabasi, Mathew H., University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I/II Study to Evaluate the Safety and Effectiveness of RevM10polAS HSCIP in Late-Stage AIDS Patients Given Intensive Myelosuppressive Conditioning.* Sponsor: Systemix Inc.

NIH/ORDA Receipt Date: 9-17-99. Not Selected for RAC Public Review: 10-7-99

9909-341 (Submission Not Complete) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD34+ Cells/Retrovirus/Antisense TAT/Transdominant Rev cDNA/Intravenous
Tisdale, John, National Institutes of Health, Bethesda, Maryland; *Low Intensity Non-Myeloablative Preparative Conditioning Followed by Transplantation of Genetically Modified HLA-Matched Peripheral Blood Hematopoietic Precursor Cells (PBPC) for Hematologic Malignancies in HIV Positive Adults*

NIH/ORDA Receipt Date: 9-20-99.

9910-342 (Open) Gene Therapy/Phase I/Other/Ulcer/In Vivo/Adenovirus/Serotype 5/Platelet Derived Growth Factor (PDGF) cDNA/Intra-Ulcer Injection

Margolis, David J., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *Phase I Trial tot Evaluate the Safety of H5.020CMVPDGF-B for the Treatment of a Diabetic Insensate Foot Ulcer.* Sponsor: Institute for Human Gene Therapy, University of Pennsylvania

NIH/ORDA Receipt Date: 10-1-99. Publicly Reviewed at the December 1999 RAC meeting.

9910-343 (Open) Gene Therapy/Phase I/Other/Ulcer/In Vivo/Adenovirus/Serotype 5/Platelet Derived Growth Factor (PDGF) cDNA/Intra-Ulcer Injection

Margolis, David J., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *Phase I Trial to Evaluate the Safety of H5.020CMVPDGF-B and Limb Compression Bandage for the Treatment of Venous Leg Ulcer (Trial A).* Sponsor: Institute for Human Gene Therapy, University of Pennsylvania

NIH/ORDA Receipt Date: 10-1-99. Publicly Reviewed at the December 1999 RAC meeting.

9910-344 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Vector-Directed Cell Lysis/In Vivo/Adenovirus Type 5/Replication-Competent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen/Intratumoral Injection

Terris, Martha K., Palo Alto Veterans Administration Medical Center, Stanford University, Palo Alto, California; *A Phase I/II Dose Finding Trial of the Intraprostatic Injection of Calydon CV787, a Prostate-Specific Antigen Cytolytic Adenovirus, in Patients with Locally Recurrent Prostate Cancer Following Definitive Radiotherapy.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 10-13-99. Not Selected for RAC Public Review: 11-2-99

9910-345 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Metastatic Prostate Cancer/Vector-Directed Cell Lysis/In Vivo/Adenovirus Type 5/Replication-Competent Virus/Promoter and Enhancer Elements of the Prostate-Specific Antigen/Intravenous Injection

Wilding, George, University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin; *A Phase I/II Dose Finding Trial of the Intravenous Injection of Calydon CV787, a Prostate-Specific Antigen Cytolytic Adenovirus, in Patients with Hormone Refractory Metastatic Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 10-13-99. Publicly Reviewed at the March 2000 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9910-346 (Open) Gene Therapy/Phase II/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Stewart, Duncan J., St. Michael's Hospital, University of Toronto, Toronto, Canada; Buller, Christopher, University of British Columbia, Vancouver, British Columbia, Canada; Rivard, Alain, University of Montreal, Montreal, Canada; Gregoire, Jean C., Montreal Heart Institute, Montreal, Canada; Page, Pierre, Hopital du Sacre-Coeur de Montreal, Montreal, Canada; Plante, Sylvain, Laval Hospital, Sainte-Foy, Canada; Archer, Stephen L., University of Alberta, Alberta, Canada; Sullivan, John, QEII Health Science Center, Halifax, Canada ; Dangoisse, Vincent, Hopital Royal Victoria Hospital, Montreal, Canada; Ducas, John, University of Manitoba, Manitoba, Canada; Hilton, J. David, Victoria Heart Institute, Victoria, Canada; Cohen, Eric A. and Bhatnagar, Gopal, Sunnybrook & Women's College Health Sciences Centre, Toronto, Canada; Langlois, Yves, Jewish General Hospital, Montreal, Quebec; Curtis, Michael, Foothills Hospital/University of Calgary, Alberta, Canada; Arnold, J. Malcolm O., University of Western Ontario, London, Ontario, Canada; Dib, Nabil, Arizona Heart Institute & Foundation; Rajakumar, A. R. J., Royal University Hospital, Saskatoon, Canada; Frank, Michael, Evanston Northwestern Healthcare, Evanston, Illinois; Lowe, James E., Duke University Medical Center, Durham, North Carolina; and Mendelsohn, Farrell O., Cardiology, P.C., Birmingham, Alabama; *A Phase II, Randomized, Multicenter, 26-Week Study to Assess the Efficacy and Safety of CI-1023 Delivered Through Minimally Invasive Surgery Versus Maximum Medical Treatment in Patients with Severe Angina, Advanced Coronary Artery Disease, and No Options for Revascularization.* Sponsor: GenVec, Inc.

NIH/ORDA Receipt Date: 10-12-99. Not Selected for RAC Public Review: 11-5-99

9910-347 (Withdrawn from RAC Review) Gene Therapy/Phase I/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Rosengart, Todd K., Northwestern Healthcare, Northwestern University, Evanston, Illinois; *Assessment of Direct Administration Via Minimally Invasive Surgery of a Replication Deficient Adenovirus Vector (Ad_{CU}VEGF.1) Containing the VEGF cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease.* Sponsor: R. Crystal, Institute of Genetic Medicine, The New York Presbyterian Hospital-Weill College of Cornell University

NIH/ORDA Receipt Date: 10-14-99. Withdrawn from RAC review: 10-16-00

9910-348 (Withdrawn from RAC Review) Gene Therapy/Phase I/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Crystal, Ronald G., Institute of Genetic Medicine, The New York Presbyterian Hospital-Weill College of Cornell University, New York, New York; *Assessment of Direct Administration Via Minimally Invasive Surgery of a Replication Deficient Adenovirus Vector (Ad_{CU}VEGF.1) Containing the VEGF cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease.*

NIH/ORDA Receipt Date: 10-14-99. Withdrawn from RAC review: 10-16-00

9910-349 (Withdrawn-replaced by protocol # 0010-427) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Sweat Duct Epithelium/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intradermal Administration

Crystal, Ronald G., Institute of Genetic Medicine, The New York Presbyterian Hospital-Weill College of Cornell University, New York, New York; *Effect of Ad_{GV}CFTR.10 on the Cystic Fibrosis Phenotype.*

NIH/ORDA Receipt Date: 10-14-99.

9910-350 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Oncogene Regulation/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intraperitoneal Administration

Alberts, David S., Arizona Cancer Center, University of Arizona, Tucson, Arizona; Wolf, Judith K., University of Texas, M.D. Anderson Cancer Center, Houston, Texas; and Muntz, Howard, Virginia Mason Medical Center, Seattle, Washington; *A Phase I Dose Escalation Study of Intraperitoneal E1A-Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer.* Sponsor: Targeted Genetics Corporation

NIH/ORDA Receipt Date: 10-14-99. Not Selected for RAC Public Review: 11-3-99

9910-351 (Open) Gene Therapy/Phase II/Cancer/Angioendothelioma/Immunotherapy/In Vivo/Plasmid DNA/Polyvinlypyrrolidone (PVP)/Human Interferon-α cDNA/Intratumoral Injection

Baker, Laurence H., University of Michigan Medical School, Ann Arbor, Michigan; *An Open-Label, Multiple Administration, Study of the Safety, Tolerability, and Efficacy of IFN-α Gene Medicine in Patients with Malignant Angioendothelioma.* Sponsor: Valentis, Inc.

NIH/ORDA Receipt Date: 10-19-99. Not Selected for RAC Public Review: 11-8-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9910-352 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1102/Leuvectin/Interleukin-2 cDNA/Intratumoral Injection

Belldegrun, Arie, University of California, Los Angeles Medical Center, Los Angeles, California; Klein, Eric A., Cleveland Clinic Foundation, Cleveland, Ohio; Corman, John, Virginia Mason Medical Center, Seattle, Washington and Moul, Judd, Walter Reed Army Medical Center, Washington, DC; *Phase I/II Study Evaluating the Safety and Efficacy of Leuvectin Immunotherapy for the Treatment of Locally Recurrent Prostate Cancer Following Radiation Therapy.* Sponsor: Vical Inc.

NIH/ORDA Receipt Date: 10-25-99. Not Selected for RAC Public Review: 11-12-99

9911-353 (Submission Not Complete) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/VEGF2-PAD-CL-009/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Annex, Brian H., Durham VA Medical Center, Durham, North Carolina; *An Open Label Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with Critical Limb Ischemia.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 11-5-99.

9911-354 (Closed) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/VEGF2-CAD-CL-005/Vascular Endothelial Growth Factor (VEGF) cDNA/Percutaneous Cardiac Catheterization

Isner, Jeffrey M., St. Elizabeth's Medical Center, Boston, Massachusetts; *A Placebo-Controlled, Dose-Escalating Study of Intramyocardial Vascular Endothelial Growth Factor 2 (VEGF2) Gene Therapy Administered Using Percutaneous Cardiac Catheterization in Patients with Class III or IV Angina.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 11-5-99. Not Selected for RAC Public Review: 1-28-00

Follow-up has been completed: 11-29-01

9911-355 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma Multiforme/Anaplastic Astrocytoma/Immunotherapy/In Vitro/Allogeneic Fibroblasts/Lethally Irradiated/Plasmid DNA-Electroporation/IR850-170/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intradermal Injection

Black, Keith L., Cedars-Sinai Medical Center, Los Angeles, California; *A Phase I, Open Label, Safety Study of Allogeneic Glioblastoma Tumor Cell Lines (IR850) Mixed with Allogeneic Fibroblasts Genetically Modified to Secrete GM-CSF (IR851) in Patients with Glioblastoma Multiforme or Anaplastic Astrocytoma.* Sponsor: The Immune Response Corporation

NIH/ORDA Receipt Date: 11-12-99. Not Selected for RAC Public Review: 2-3-00

9911-356 (Closed) Gene Therapy/Phase I/Cancer/MUC-1 Expressing Tumors/Immunotherapy/In Vivo/Vaccinia Virus/TG4010.01/MUC-1/Interleukin-2/Intramuscular Injection

Figlin, Robert and Belldegrun, Arie, University of California, Los Angeles Medical Center, Los Angeles, California; *Phase I Bridging Trial of TG4010 as Antigen-Specific Immunotherapy in Patients with MUC-1 Positive Advanced Cancer.* Sponsor: Transgene, Inc.

NIH/ORDA Receipt Date: 11-16-99. Not Selected for RAC Public Review: 12-6-99

Completed: 9-11-00

9911-357 (Open) Gene Therapy/Phase I-II/Cancer Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1102/Leuvectin/Interleukin-2 cDNA/Intratumoral Injection

Galanis, Evanthia, Mayo Clinic, Rochester, Minnesota; and Hawkins, Michael, Washington Hospital Center, Washington Cancer Institute, Washington, D.C.; *Protocol for Retreatment with Leuvectin Immunotherapy for Cancer.* Sponsor: Vical Inc.

NIH/ORDA Receipt Date: 11-18-99. Not Selected for RAC Public Review: 12-8-99

9911-358 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Liver/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Interleukin-12 cDNA/Intratumoral Injection

Sung, Max W. and Woo, Savio L. C., Mount Sinai School of Medicine, New York, New York; *Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12 cDNA by Intratumoral Injection in Patients with Metastatic Breast Cancer to the Liver.*

NIH/ORDA Receipt Date: 11-22-99. Publicly Reviewed at the March 2000 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9911-359 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Liver/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Interleukin-12 cDNA/Intratumoral Injection

Sung, Max W. and Woo, Savio L. C., Mount Sinai School of Medicine, New York, New York; *Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12 cDNA by Intratumoral Injection in Patients with Primary or Metastatic Colorectal Cancer to the Liver.*

NIH/ORDA Receipt Date: 11-22-99. Publicly Reviewed at the March 2000 RAC meeting

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9912-360 (Open) Gene Marking/Cancer/Melanoma/In Vitro/Syngeneic Peripheral Blood Lymphocytes/Retrovirus/Neomycin Phosphotransferase Gene/Intravenous Infusion

Rosenberg, Steven A., National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Metastatic Melanoma Using Cloned Lymphocytes Following the Administration of a Nonmyeloablative But Lymphocyte Depleting Regimen.*

NIH/ORDA Receipt Date: 11-22-99. Not Selected for RAC Public Review: 12-31-99

9912-361 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/B7 (CD80), HLA-A1 or A2 cDNAs/Subcutaneous Injection

Podack, Eckhard R., Cassileth, Peter A., Sridhar, Kasi, and Savaraj, Niramol, University of Miami, Miami, Florida; *Elicitation of a Cellular Immune Response in Patients with Non-Small Cell Lung Cancer by Immunogenic Tumor Cell Vaccination - A Phase I Study.*

NIH/ORDA Receipt Date: 12-1-99. Not Selected for RAC Public Review: 12-21-99

9912-362 (Open) Gene Marking/Cancer/Melanoma/In Vitro/Syngeneic Peripheral Blood Lymphocytes/Retrovirus/Neomycin Phosphotransferase Gene/Intravenous Infusion

Rosenberg, Steven A., National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Metastatic Melanoma Using Cloned Peripheral Blood Lymphocytes Sensitized In Vitro to the gp209-2M Immunodominant Peptide*

NIH/ORDA Receipt Date: 12-16-99. Not Selected for RAC Public Review: 1-7-00

9912-363 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Penile Carcinoma/Vector-Directed Cell Lysis/Replication-Competent Virus/Pro-Drug/In Vivo/adenovirus/Serotype 5/E. coli Cytosine deaminase Gene/Herpes Simplex Thymidine Kinase cDNA/Valacyclovir/Intratumoral Injection

Miles, Brian J., Ayala, Gustavo, and Aguilar-Cordova, Estuardo, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas; *Phase I Study of the Replication-Competent, E1B-Attenuated Adenovirus with a CD/HSV-1 TK Fusion Gene and the Oral Administration of Valacyclovir in Adults with Penile Cancer.*

NIH/ORDA Receipt Date: 12-20-99. Publicly Reviewed at the March 2000 RAC meeting

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9911-364 (Open) Gene Therapy/Phase I-II/Infectious Disease/Epstein-Barr Virus (EBV) and Cytomegalovirus Diseases/In Vitro/EBV and CMV-Specific Cytotoxic T Lymphocytes/Retrovirus/Cytomegalovirus pp65 Gene/Intravenous

Lucas, Kenneth G., University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I-II Trial to Examine the Toxicity of CMV and EBV Specific Cytotoxic T Lymphocytes When Used for Prophylaxis Against EBV and CMV Disease in Recipients of CD34+ Selected/T Cell Depleted Stem Cell Transplants.*

NIH/ORDA Receipt Date: 11-26-99. Not Selected for RAC Public Review: 1-3-00

9912-365 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD4+ T Cells/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous Infusion

Aronson, Naomi, Walter Reed Army Medical Center, Washington, D.C.; *A Phase I/II Study of the Safety, Survival, and Trafficking of Autologous CD4-zeta Gene-Modified T Cells With and Without Exogenous Interleukin-2 in HIV-Infected Patients.* Sponsors: University of Pennsylvania and Cell Genesys, Inc.

NIH/ORDA Receipt Date: 12-22-99. Not Selected for RAC Public Review: 4-14-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9912-366 (Open)Gene Therapy/Phase III/Cancer/Squamous Cell Carcinoma of the Head and Neck (SCCHN)/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5 p53 cDNA/Intratumoral Injections

Hamm, John T., University of Louisville, Norton Healthcare, Louisville, Kentucky; Haigentz, Missak, Montefiore Medical Center, Bronx, New York; Arquette, Mathew, Washington University School of Medicine, Barnard Cancer Center, St. Louis, Missouri; Cullen, Kevin J., Georgetown University Medical Center, Washington, D.C.; Goodwin, W. Jarrard, University of Miami, Miami, Florida; Flood, William A., The Milton S. Hershey Medical Center, Hershey, Pennsylvania; Yoo, George University Health Center, Detroit, Michigan; and Krempl, Greg, The University of Oklahoma, Oklahoma City, Oklahoma; Turpeenniemi-Hujanen, Taina, OULU University Hospital, Oulu, Finland; Kellokumpu-Lehtinen, Pirkko, Tampere University Hospital, Tampere, Finland; Brockstein, Bruce, Evanston Northwestern Healthcare, Evanston, Illinois; Cobb, Patrick, Billings Oncology Associates, Billings, Montana; Williamson, Stephen, University of Kansas Medical Center, Kansas City, Kansas; Burkey, Brian, The Vanderbilt Clinic/Vanderbilt University Medical Center, Nashville, Tennessee; Carrato Mena, Alfredo, Hospital General De Elche, Elche (Spain); Barnadas, Agusti, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; Trigo, J. Ma., Hospital General Vall d'Hebron, Barcelona, Spain; Cortes-Funes, Hernan, Hospital 12 de Octubre, Madrid, Spain; Constenla, Manuel, Complejo Hospitalario De Pontevedra, Pontevedra, Spain; Sanchez, Emilio Fonseca, Hospital Clinico de Salamanca, Salamanca, Spain; Ruiperez, Andres Cervantes, Hospital Clinico Universitaro, Valencia, Spain; Guillem, Vicente, Instituto Valenciano de Oncologia, Valencia, Spain; Nathan, Cherie-Ann, Louisiana State University, Shreveport, Louisiana; Agarwala, Sanjiv, University of Pittsburgh, Pittsburgh, Pennsylvania; Rosen, Fred, The University of Illinois at Chicago, Chicago, Illinois; Breau, Randall, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Giguere, Jeffrey, Cancer Center of the Carolinas, Greenville, South Carolina; Trask, Douglas, University of Iowa Hospitals and Clinics, Iowa City, Iowa; Zitsch, Robert, University of Missouri Health Care, Columbia, Missouri; Hrushesky, William, J. M., Dorn Veterans Affairs Medical Center, Columbia, South Carolina; Clayman, Gary, University of Texas, MD Anderson Cancer Center, Houston, Texas; Guthrie, Troy H., Jr., University of Florida, Jacksonville, Florida; Slolomon, William, SUNY Health Science Center at Brooklyn, Brooklyn, New York; Law, Amy, Geisinger Medical Center, Danville, Pennsylvania; Trask, Douglas, University of Iowa Health Care, Iowa City, Iowa; Nemechek, Andrew, Tulane University School of Medicine, New Orleans, Louisiana; Villaret, Douglas, University of Florida, Gainesville, Florida; Van Echo, David, University of Maryland School of Medicine, Baltimore, Maryland; McCaffrey, Thomas V., H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; Wheeler, Richard H., Huntsman Cancer Institute, Salt Lake City, Utah; Chen, Amy, Emory University, Atlanta, Georgia; and Gal, Thomas, Jr., University of Washington Medical Center, Seattle, Washington; *A Phase III Multi-Center, Open-Label, Randomized Study to Compare the Overall Survival and Safety of Bi-Weekly Intratumoral Administration of INGN 201 Versus Weekly Methotrexate in 240 Patients with Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Aventis Pharmaceuticals - Gencell Division (formerly Rhone-Poulenc Rorer)

NIH/ORDA Receipt Date: 12-28-99. Publicly Reviewed at the March 2000 RAC meeting

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9912-367 (Open) Gene Therapy/Phase I/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Total Tumor RNA/Intravenous

Vieweg, Johannes, Duke University Medical Center, Durham, North Carolina; *Active Immunotherapy of Metastatic Renal Cell Carcinoma Using Autologous Dendritic Cells Transfected with Autologous Renal Tumor RNA.*

NIH/ORDA Receipt Date: 12-28-99. Not Selected for RAC Public Review: 1-14-00

9912-368 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen/B7.1 (CD80)/Intramuscular or Intradermal Injection

Dahut, Bill, National Naval Medical Center, Bethesda, Maryland; and Gulley, James, National Institutes of Health, Bethesda, Maryland; *A Randomized Phase II Study of a PSA-Based Vaccine in Patients with Localized Prostate Cancer Receiving Standard Radiotherapy.*

NIH/ORDA Receipt Date: 12-29-99. Not Selected for RAC Public Review: 3-7-00

0001-369 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Myelodysplasia or Acute Myelogenous Leukemia (AML)/In Vitro/Autologous Acute Myeloblastic Leukemia Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) cDNA/Subcutaneous or Intradermal Injection

DeAngelo, Daniel J., Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Study of Vaccination with Lethally Irradiated, Autologous Acute Myeloblastic Leukemia Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor in Patients with Advanced Myelodysplasia or Acute Myelogenous Leukemia.*

NIH/OBA Receipt Date: 1-3-00. Not Selected for RAC Public Review: 1-24-00

0001-370 (Open) Gene Therapy/Phase I/Monogenic Disease/Fanconi Anemia/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Fanconi Anemia Complementation Group A and C cDNA/Intravenous

Croop, James M., Indiana University School of Medicine, Indianapolis, Indiana; *Gene Therapy for Patients with Fanconi Anemia: A Pilot Study.*

NIH/OBA Receipt Date: 1-6-00. Not Selected for RAC Public Review: 2-4-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0001-371 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Monogenic Disease/Hemophilia B/In Vivo/Adeno-Associated Virus/Factor IX Gene/Intrahepatic Artery Administration

Glader, Bertil, Stanford University, Stanford, California; and Manno, Catherine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; *A Phase I Safety Study in Patients with Severe Hemophilia B (Factor IX Deficiency) Using Adeno-Associated Viral Vector to Deliver the Gene for Human Factor IX into the Liver.*

NIH/OBA Receipt Date: 1-7-00. Publicly Reviewed at the March 2000 RAC meeting

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0001-372 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Monogenic Disease/Hemophilia A/In Vivo/Helper-Dependent (Gutted) Adenovirus/Factor VIII cDNA/Intravenous Injection

White II, Gilbert, University of North Carolina School of Medicine, Chapel Hill, North Carolina; Thompson, Arthur, University of Washington, Seattle, Washington; and Gruppo, Ralph A., Children's Hospital Medical Center, Cincinnati, Ohio; *A Phase 1, Single-Dose, Dose-Escalation Study of MiniAdFVIII Vector in Patients with Severe Hemophilia A.* Sponsor: Corautus Genetics, Inc. (formerly GenStar Therapeutics Corporation)

NIH/OBA Receipt Date: 1-12-00. Publicly Reviewed at the September 2000 RAC meeting

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0001-373 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen/B7.1 (CD80)/Intramuscular or Intradermal Injection

Arlen, Philip M., National Naval Medical Center and National Institutes of Health, Bethesda, Maryland; *A Randomized Phase II Study of Either Immunotherapy with a Regimen of Recombinant Pox Viruses that Express PSA/B7.1 Plus Adjuvant GM-CSF and IL-2 or Hormone Therapy with Nilutamide in Patients with Hormone Refractory Prostate Cancer and No Radiographic Evidence of Disease.*

NIH/OBA Receipt Date: 1-10-00. Not Selected for RAC Public Review: 3-7-00

0001-374 (Withdrawn-replaced by 0007-407) Gene Therapy/Phase I/Coronary Artery Disease/In Vivo/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Cardiac Administration

A Phase I Open Label, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention and the related follow-up study *A Phase I Open Label, Multi-Center Extension Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention.* Sponsor: Genzyme Corporation.

NIH/OBA Receipt Date: 1-13-00.

0001-375 (Withdrawn-replaced by protocol # 0010-425) Gene Therapy/Phase I/Other Disorders/Hip Fracture/In Vivo/Plasmid DNA/Collagen Sponge/Parathyroid Hormone cDNA/Bone Administration

A Phase I Safety, Tolerance and Pharmacokinetic Study of Mat-100 in Elderly Patients with Fresh Fracture of the Hip. Sponsor: Selective Genetics, Inc.

NIH/OBA Receipt Date: 1-13-00.

0001-376 (Open) Gene Therapy/Phase I/Cancer/Non-Hodgkin's Lymphoma/Chemoprotection/Fusion Gene of a Mutant Dihydrofolate Reductase and Cytidine Deaminase/In Vitro/Autologous Peripheral Blood CD34+ Cells/Retrovirus/Intravenous Infusion

Bertino, Joseph, Memorial Sloan Kettering Cancer Center, New York, New York; *A Gene Therapy Based Myeloprotection Strategy Using a Mutant Dihydrofolate Reductase - Cytidine Deaminase Fusion Gene for the Treatment of Refractory or Relapsed Non-Hodgkin's Lymphoma.*

NIH/OBA Receipt Date: 1-13-00. Not Selected for RAC Public Review: 2-3-00

0001-377 (Withdrawn from RAC Review) Gene Therapy/Phase I/Monogenic Disease/Fabry Disease/In Vitro/Autologous Mesenchymal Stem Cells/Retrovirus/α-Galactosidase A cDNA/Immunoisolation Device/Subcutaneous Implantation

Medin, Jeffrey A., University of Illinois at Chicago, Chicago, Illinois; *A Phase I Trial of Retroviral Transduction of Autologous Mesenchymal Stem Cells from Patients with Fabry Disease with Alpha-Galactosidase A cDNA and Implantation Via an Immunoisolation Device.* Sponsor: Osiris Therapeutics, Inc.

NIH/OBA Receipt Date: 1-13-00. Withdrawn from RAC review: 3-1-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0002-378 (Open) Gene Therapy/Phase II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Interferon-α/Interleukin-12 cDNA/Intratumoral Injection

McQuone, Shelly J., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *A Multicenter, Open-Label, Multiple Administration, Study of the Safety, Tolerability and Efficacy of IFNα/IL-12 Combination Gene Therapy in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 2-9-00. Not Selected for RAC Public Review: 8-8-00

0001-379 (Submission Not Complete) Gene Therapy/Phase I/Immunotherapy/Cancer/Colon/Adenovirus/Serotype 5/GA733-2 Antigen cDNA/Intradermal Injection

Eck, Stephen L., University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Phase I Trial of Intradermal Adenovirus GA733 Vaccine for Advanced Colorectal Cancer.*

NIH/OBA Receipt Date: 1-13-00.

0001-380 (Under Review) Gene Therapy/Phase I/Monogenic Disease/Amyotrophic Lateral Sclerosis/In Vivo/Adeno-Associated Virus/Excitatory Amino Acid Transporter 2 (EAAT2) cDNA/Percutaneous Cervical Injection

During, Matthew J. and Simeone, Frederick A., Thomas Jefferson University, Philadelphia, Pennsylvania; *Clinical Trial in Amyotrophic Lateral Sclerosis Patients Using Gene Transfer of the EAAT2 Gene in the Cervical Spinal Cord.*

NIH/OBA Receipt Date: 1-13-00. Review at a RAC meeting pending; investigators have requested postponement of public review.

0001-381 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Monogenic Disease/Canavan Disease/In Vivo/Adeno-Associated Virus/Aspartoacylase cDNA/Stereotactic Intracranial Administration

Leone, Paola and Feely, Michael, Cooper Health System, Camden, New Jersey; *Gene Therapy of Canavan Disease using AAV for Brain Gene Transfer.*

NIH/OBA Receipt Date: 1-13-00. Publicly Reviewed at the March 2000 RAC meeting

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0001-382 Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Autologous Neuroblastoma Cells/Lethally Irradiated/Adenovirus/Serotype 5/Interleukin-2 cDNA/Subcutaneous Injection

Russell, Heidi, Baylor College of Medicine, Houston, Texas; *A Pilot Study of Gene Modified Autologous Neuroblastoma Vaccine for the Post-Chemotherapy Treatment of High Risk Neuroblastoma.*

NIH/OBA Receipt Date: 1-14-00.

0001-383 (Withdrawn) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Catheterization

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Phase IIb Multicenter, Randomized, Controlled Study of Direct Intramyocardial Injection of pVGI.1 (VEGF2) Versus Maximum Medical Therapy in Patients with Class III or IV Angina.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/OBA Receipt Date: 1-18-00.
Withdrawn from consideration, no individuals enrolled: 11-29-01

0001-384 (Withdrawn) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Catheterization

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Double-Blind, Placebo-Controlled, Continuation Study of Intramyocardial pVGI.1 (VEGF2) Administered by Percutaneous Cardiac Catheterization in Patients with Class III or IV Angina.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/OBA Receipt Date: 1-18-00.
Withdrawn from consideration, no individuals enrolled: 11-29-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0001-385 (Open) Gene Therapy/Phase I-II/Immunotherapy/Cancer/Non-Small Cell Lung Carcinoma (NSCLC)/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Smith II, John W., Providence Portland Medical Center, Portland, Oregon; Jablons, David, University of California, San Francisco, San Francisco, California; and Sterman, Daniel, University of Pennsylvania, Philadelphia, Pennsylvania; *Phase I/II Study of GM-CSF Gene-Modified Autologous Tumor Vaccines in Early and Advanced Stage Non-Small Cell Lung Cancer (NSCLC).* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 1-20-00. Not Selected for RAC Public Review: 2-9-00

0001-386 (Open) Gene Therapy/Phase II/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Irradiated/Canarypox Virus/B7.1 (CD80) cDNA/Subcutaneous Injection

Antonia, Scott J., H. Lee Moffitt Cancer Center, University of South Florida, Tampa, Florida; *Phase II Study of a B-7.1 Gene Modified Autologous Tumor Cell Vaccine and Systemic IL-2 for Patients with Stage IV Renal Cell Carcinoma.*

NIH/OBA Receipt Date: 1-24-00. Not Selected for RAC Public Review: 2-29-00

0001-387 (Open) Gene Therapy/Phase II/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Kornowski, Ran, Cardiovascular Research Institute, Washington, D.C.; Dib, Nabil, Arizona Heart Institute & Foundation, Phoenix, Arizona; Cohen, Barry M., Morristown Memorial Hospital, Morristown, New Jersey; and Moses, Jeffrey W., Lenox Hill Heart Hospital, New York, New York; *A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 12-Week Follow-up, Pilot Study of the Tolerability and Feasibility of Administering $AD_{GV}VEGF_{121.10}$ (CI-1023) Via the Biosense Intramyocardial Injection Device to Patients with Advanced Coronary Artery Disease.* Sponsor: GenVec, Inc.

NIH/OBA Receipt Date: 1-27-00. Not Selected for RAC Public Review: 2-24-00

0002-388 (Open) Gene Therapy/Phase II/Other/Peripheral Arterial Disease/In Vivo/Ischemic Lower Limb/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Intramuscular Injection

Rajagopalan, Sanjay, University of Michigan Medical Center, Ann Arbor, Michigan; Chaikof, Elliot, Emory University School of Medicine, Atlanta, Georgia; Deitcher, Steven, The Cleveland Clinic Foundation, Cleveland, Ohio; Rhee, Robert Y., University of Pittsburgh, Pittsburgh, Pennsylvania; Corson, John D., The University of Iowa Hospitals and Clinics, Iowa City, Iowa; Mohler, Emile R., University of Pennsylvania Health System, Philadelphia, Pennsylvania; Jaff, Michael, Cardiovascular Research Institute, Washington, DC; Goldman, Corey K., Watson Clinic Center for Research, Lakeland, Florida; Blebea, John, Penn State College of Medicine, Hershey, Pennsylvania; Hirsch, Alan T., University of Minnesota, Minneapolis, Minnesota; Annex, Brian H., Duke University Medical Center, Durham, North Carolina; Guzman, Raul, Vanderbilt University Medical Center, Nashville, Tennessee; Tenaglia, Alan, Tulane University Health Sciences Center, New Orleans, Louisiana; Azrin, Michael, University of Connecticut Health Center, Farmington, Connecticut; Gagne, Paul, New York University School of Medicine, New York, New York; Dib, Nabil, Arizona Heart Institute & Foundation, Phoenix, Arizona; Garza, Luis, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Hermiller, James, The Care Group, Indianapolis, Indiana; Mendelsohn, Farrell, Baptist Health System, Birmingham, Alabama; Miller, Julie M., Johns Hopkins University, Baltimore, Maryland; Anderson, R. David, Sarasota Memorial Healthcare System, Sarasota, Florida; and Davies, Mark G., University of Rochester Medical Center, Rochester, New York; *A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 ($AD_{GV}VEGF_{121.10}$) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication.* Sponsor: GenVec, Inc.

NIH/OBA Receipt Date: 2-2-00. Not Selected for RAC Public Review: 3-27-00

0002-389 (Open) Gene Therapy/Phase I/Cancer/Liver Metastasis of Colorectal Carcinoma/Immunotherapy/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Interleukin-2 cDNA/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Sung, Max W., Mount Sinai School of Medicine, New York, New York; *Phase I/IB Trial of Combination Adenoviral Vector Delivery of the Human Recombinant Interleukin-2 Gene and the Herpes Simplex Virus Thymidine Kinase Gene by Intratumoral Injection and Followed by Intravenous Ganciclovir in Patients with Hepatic Metastases from Colorectal Cancer.*

NIH/OBA Receipt Date: 2-4-00. Not Selected for RAC Public Review: 3-10-00

0003-390 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD 34+ Hematopoietic Stem Cells/Retrovirus/Transdominant Rev/Intravenous Infusion

Kohn, Donald B., Childrens Hospital Los Angeles, University of Southern California, Los Angeles, California; *Retroviral-Mediated Transfer of the RevM10 and FX Genes into CD 34+ Cells from the Bone Marrow of HIV-1 Infected Children.*

NIH/OBA Receipt Date: 3-1-00. Not Selected for RAC Public Review: 3-21-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0002-391 (Closed) Gene Therapy/Phase II/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical-1102/Leuvectin/Interleukin-2 cDNA/Intratumoral Injection/Vical Protocol VCL-1102-204

Thompson, John A., University of Washington School of Medicine, Seattle, Washington; Hawkins, Michael, Washington Hospital Center, Washington Cancer Institute, Washington, D.C.; Figlin, Robert A., University of California Los Angeles Medical Center, Los Angeles, California; Lee, Fa-Chyi, University of New Mexico Cancer Research and Treatment Center and University Hospital, Albuquerque, New Mexico; Ernstoff, Marc S., Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; Bukowski, Ronald, The Cleveland Clinic Foundation, Cleveland, Ohio; Morse, Michael A., Duke University Medical Center, Durham, North Carolina; and Amato, Robert, Baylor College of Medicine, Houston, Texas; *Phase II Study of Leuvectin in Patients with Metastatic Renal Cell Carcinoma.* Sponsor: Vical Inc.

NIH/OBA Receipt Date: 2-14-00. Not Selected for RAC Public Review: 3-6-00

Notification from sponsor that study is closed: 6-29-01.

0003-392 (Closed) Gene Therapy/Phase I-II/Cancer/Non-Hodgkin's B-Cell Lymphoma/Mantle Cell Lymphoma/Immunotherapy/In Vivo/Naked Plasmid DNA/Tumor Idiotype/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intramuscular and Intradermal Injections/Vical Protocol VCL-1642-101

Levy, Ronald, Stanford University School of Medicine, Stanford, California; *Phase I/II Study of Vaccine Therapy for B-Cell Lymphoma Utilizing Plasmid DNA Coding for Tumor Idiotype.* Sponsor: Vical Inc.

NIH/OBA Receipt Date: 3-17-00. Not Selected for RAC Public Review: 4-6-00

0004-393 (Open) Gene Therapy/Phase II/Cancer/Non-Small Cell Lung Cancer/Antisense/In Vitro/Allogeneic Tumor Cells/Irradiated/Plasmid DNA-Electroporation/TGF-β/Subcutaneous Injection

Sobol, Robert and Bodkin, David, Sharp Health Care, Sidney Kimmel Cancer Center, San Diego, California; Batra, Raj K., University of California, Los Angeles and West Los Angeles Veteran's Administration Medical Center, Los Angeles, California; and Dillman, Robert O., Hoag Cancer Center, Newport Beach, California; *Phase II Study of a TGF-β2 Antisense Gene Modified Allogeneic Tumor Cell Vaccine in Patients with Stages II-IV Non-Small Cell Lung Cancer.* Sponsor: NovaRx

NIH/OBA Receipt Date: 4-3-00. Not Selected for RAC Public Review: 5-2-00

0005-394 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Naked Plasmid/Tyrosinase cDNA/Intramuscular Injection

Wolchok, Jedd, Memorial Sloan-Kettering Cancer Center, New York, New York; *Vaccination of AJCC Stage III and IV Melanoma Patients with Human and Mouse Tyrosinase DNA Vaccines: A Phase I Trial to Assess Safety and Immune Response.*

NIH/OBA Receipt Date: 5-1-00. Not Selected for RAC Public Review: 5-19-00

0005-395 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vivo/Adenovirus/Type 5/MART-1 Melanoma Antigen/gp100 Melanoma Antigen/Intradermal Injection

Haluska, Frank G, Harvard Medical School, Boston, Massachusetts; Cunningham, Charles, US Oncology, Dallas, Texas; Ernstoff, Marc, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; and Richards, Jon M., Oncology Specialists, S. C., Chicago, Illinois; *A Phase I/II Trial Investigating the Safety and Immunogenicity of Adenoviruses Encoding the Melan-A/MART-1 and gp100 Melanoma Antigens Administered Intradermally to Patients with Stage II-IV Melanoma.* Sponsor: Genzyme Corporation

NIH/OBA Receipt Date: 5-1-00. Not Selected for RAC Public Review: 9-14-00

0005-396 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Colon Carcinoma (Hepatic Metastasis)/Herpes Simplex Virus Type 1/Tumor Lysis/Intrahepatic Artery Administration

Fong, Yuman, Memorial Sloan Kettering Cancer Center, New York, New York; *A Phase I, Open -Label, Dose-Escalating Study of the Safety, Tolerability, and Anti-tumor Activity of a Single Intrahepatic Injection of a Genetically Engineered Herpes Simplex Virus, NV1020, in Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver* and the associated, long-term follow-up protocol: *Long-Term Follow-Up of the Safety and Survival of subjects with Adenocarcinoma of the Colon with Metastasis to the Liver Who Enrolled in a Phase I Dose-Escalating Study Evaluating a Genetically Engineered Herpes Simplex Virus, NV1020.* Sponsor: NeuroVir Therapeutics, Inc.

NIH/OBA Receipt Date: 5-2-00. Publicly Reviewed at the June 2000 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0005-397 (Open) Gene Therapy/Phase I/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration (Catheter)

Sanborn, Timothy A., Joan and Sanford I. Weill Medical College, Cornell University, New York, New York; *A Feasibility Study of Catheter-Based Administration of a Replication Deficient Adenovirus Vector ($Ad_{cu}VEGF.1$) to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease.* Sponsor: R. Crystal, M.D.

NIH/OBA Receipt Date: 5-3-00. Not Selected for RAC Public Review: 5-23-00

0005-398 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/In Vivo/Tropism-Modified Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Somatostatin Receptor cDNA/Ganciclovir/Intraperitoneal Injection

Barnes, Mack N., University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Study of a Tropism Modified Adenovirus Vector for Intraperitoneal Delivery of Therapeutic Genes in Ovarian and Extraovarian Cancer Patients.*

NIH/OBA Receipt Date: 5-3-00. Publicly Reviewed at the December 2000 RAC meeting

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0005-399 (Open) Gene Therapy/Phase I/Cancer/Solid Tumors/Immunotherapy/In Vivo/Adenovirus/Type 5/Tumor Necrosis Factor cDNA/Intratumoral Injection

Guha, Chandan and Mani, Sridhar, Albert Einstein College of Medicine, Bronx, New York; Hanna, Nader, University of Kentucky Medical Center, Lexington, Kentucky; Nemunaitis, John, US Oncology, Dallas, Texas; Richards, Donald A., Tyler Cancer Center, Tyler, Texas; and Rosemurgy, Alexander, University of South Florida, Tampa, Florida; *An Open-Label, Phase I, Dose-Escalation Study of Tumor Necrosis Factor-alpha (TNFerade™ Biologic) Gene Therapy with Radiation Therapy for Locally Advanced, Recurrent, or Metastatic Solid Tumors.* Sponsor: GenVec

NIH/OBA Receipt Date: 5-3-00. Not Selected for RAC Public Review: 5-23-00

0005-400 (Open) Gene Therapy/Phase I/Cancer/Lymphoma/Chemoprotection/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Intravenous Infusion

Becker, Pamela S., University of Massachusetts Memorial Health Care, Worcester, Massachusetts; *Transfer of the Multidrug Resistance Gene, MDR-1, to Hematopoietic Progenitors from Patients with High Risk Lymphoma.*

NIH/OBA Receipt Date: 5-3-00. Not Selected for RAC Public Review: 6-5-00

0005-401 (Open) Gene Therapy/Phase II/Cancer/Chronic Lymphocytic Leukemia/Immunotherapy/In Vitro/Autologous Leukemic Cells/Adenovirus/Serotype 5/CD154 cDNA/Intravenous Infusion

Gribben, John, Dana-Farber Cancer Institute, Boston, Massachusetts; and Saville, M. Wayne, University of California-San Diego Medical Center, San Diego, San Diego, California; *Open-Label, Multicenter, Phase II Study of Autologous Ad-CD154 Expressing Transduced CLL Cells in B Cell Chronic Lymphocytic Leukemia Subjects Enrolled in Two Parallel Arms.* Sponsor: Tragen Pharmaceuticals (formerly Immunogenex, Inc.)

NIH/OBA Receipt Date: 5-3-00. Not Selected for RAC Public Review: 5-23-00

0006-402 (Closed) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Autologous T Lymphocytes/Plasmid DNA/Electroporation/CE7R-Specific scFvFc-Zeta T Cell Receptor/Intravenous Infusion

Jensen, Michael, City of Hope National Medical Center, Duarte, California; *Phase I Study to Evaluate the Safety of Cellular Immunotherapy for Recurrent/Refractory Neuroblastoma Using Genetically-Modified Autologous CD8+ T Cell Clones.*

NIH/OBA Receipt Date: 6-2-00. Not Selected for RAC Public Review: 6-22-00

0006-403 (Open) Gene Therapy/Phase IIb/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Fibroblast Growth Factor (FGF) cDNA/Intracoronary Administration

Iskandrian, Ami E., University of Alabama at Birmingham, Birmingham, Alabama; Churchill, David, North West Arkansas Heart and Vascular Center, Fayetteville, Arkansas; Gammon, Roger S., Austin Heart, P.A., Austin, Texas; Ghali, Jalal K., Cardiac Centers of Louisiana, LLC, Shreveport, Louisiana; Grines, Cindy L., William Beaumont Hospital, Royal Oak, Michigan; Helmer, Gregory A., Minnesota Heart Clinic, P. A., Edina, Minnesota; Kleiman, Neal, S., Baylor College of Medicine, Houston, Texas; Rade, Jeffrey J., The Johns Hopkins Hospital, Baltimore, Maryland; Rowe, Steven K., Heartland Health Center, St. Joseph, Missouri; Watkins, Matthew W., Fletcher Allen Health Care, Burlington, Vermont; and Uretsky, Barry, University of Texas, Galveston, Galveston, Texas; *A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effect of Ad5FGF-4 on Myocardial Perfusion Defect Size and Safety in Patients with Stable Angina.* Sponsor: Berlex Laboratories

NIH/OBA Receipt Date: 6-5-00. Not Selected for RAC Public Review: 8-18-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0006-404 (Closed, RAC Reviewed with Recommendations) Gene Therapy/Phase II/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) cDNA/Aerosol Administration

Moss, Richard B., Stanford University School of Medicine, Palo Alto, California; Waltz, David, Children's Hospital, Boston, Massachusetts; Rodman, David, University of Colorado Health Sciences Center, Denver, Colorado; Spencer, L. Terry, Virella-Lowell, Isabel, Brantly, Mark, and Flotte, Terry, University of Florida, Gainesville, Florida; Zeitlin, Pamela, Johns Hopkins University, Baltimore, Maryland; Aitken, Moira, University of Washington, Seattle, Washington; Milla, Carlos, University of Minnesota, Minneapolis, Minnesota; and Clancy, John Paul, University of Alabama at Birmingham, Birmingham, Alabama; *A Multicenter, Double-Blind, Placebo-Controlled, Phase II Study of Aerosolized AAVCF in Cystic Fibrosis Patients with Mild Lung Disease.* Sponsor: Targeted Genetics

NIH/OBA Receipt Date: 6-12-00. Publicly Reviewed at the September 2000 RAC meeting
Enrollment is complete: 10-3-02

0006-405 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD 80)/ICAM-1/LFA-3/Intramuscular Or Intradermal Injection

Marshall, John L., Georgetown University Medical Center, Washington, D.C.; *A Phase I Study of Sequential Vaccinations with Fowlpox-CEA(6D)-TRICOM (B7.1/ICAM-1/LFA-3) Alone, OR in Combination with Vaccinia-CEA(6D)-TRICOM, and the Role of GM-GSF, in Patients with CEA Expressing Carcinomas.*

NIH/OBA Receipt Date: 6-12-00. Not Selected for RAC Public Review: 11-7-00

0006-406 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Anemia of End Stage Renal Disease (ESRD)/In Vitro/Autologous Vascular Smooth Muscle Cells/Retrovirus/Erythropoietin (EPO) cDNA/Vascular Grafts Lined with Transduced Smooth Muscle Cells

Muczynski, Kimberly A. and Osborne, William R. A., University of Washington School of Medicine, Seattle, Washington; *Erythropoietin Administration in Hemodialysis Patients Using Vascular Grafts Lined with Transduced Smooth Muscle Cells.*

NIH/OBA Receipt Date: 6-13-00. Publicly Reviewed at the September 2000 RAC meeting

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0007-407 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Coronary Artery Disease/In Vivo/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Cardiac Administration/CAD-HIF-004-99

Rosengart, Todd K, Northwestern University Medical School, Evanston, Illinois; McCurry, Kenneth, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Cmolik, Brian L., University Hospitals of Cleveland, Cleveland, Ohio; Landolfo, Kevin P., Duke University Medical Center, Durham, North Carolina; Dullum, Mercedes, Washington Hospital Center, Washington, DC; Lattouf, Omar, Emory University School of Medicine, Atlanta, Georgia; Fontana, Gregory, Cedars-Sinai Medical Center, Beverly Hills, California; Chronos, Nicolas, Atlanta Cardiology Research Institute, Atlanta, Georgia; and Henry, Timothy, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; *A Phase I, Double-blind, Placebo Controlled, Escalating Dose, Multi-center Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administration by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention.* Sponsor: Genzyme Corporation

NIH/OBA Receipt Date: 7-31-00. Publicly Reviewed at the September 2000 RAC meeting

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0007-408 (Open) Gene Therapy/Phase I-II/Cancer/B-Cell Chronic Lymphocytic Leukemia/Immunotherapy/In Vivo/Naked Plasmid DNA/Tumor Idiotype/Intramuscular Injection

Garcia-Manero, Guillermo, University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I/II Study of Idiotypic Vaccination for Chronic Lymphocytic Leukemia using a Genetic Approach.*

NIH/OBA Receipt Date: 7-31-00. Not Selected for RAC Public Review: 8-18-00

0007-409 (Open) Gene Therapy/Phase I/Cancer/Lung Cancer/Immunotherapy/In Vivo/Cationic Liposome Complex/Interleukin-2 cDNA/Intravenous Injection

Hainsworth, John Daniel, Sarah Cannon Cancer Center, Centennial Medical Center, Nashville, Tennessee; and Antonia, Scott, H. Lee Moffitt Cancer Center, Tampa, Florida; *A Phase I, Multi-Center, Open-Label, Dose-Escalation Study of the Safety and Tolerability of Intravenously Administered VLTS-587 in Patients with Solid Tumors and the Presence of Metastases or Primary Cancer in the Lungs.* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 7-28-00. Not Selected for RAC Public Review: 9-7-00

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0008-410 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Total Tumor RNA/Intravenous

Vieweg, Johannes, Duke University, Durham, North Carolina; *A Safety and Feasibility Study of Active Immunotherapy in Patients with Metastatic Prostate Carcinoma Using Autologous Dendritic Cells Pulsed with Antigen Encoded in Amplified Autologous Tumor RNA.*

NIH/OBA Receipt Date: 8-22-00. Not Selected for RAC Public Review: 9-12-00

0009-411 (Closed, RAC Reviewed with Recommendations) Gene Therapy/Phase I/Other Disorders/Restenosis/In Vivo/Vascular Smooth Muscle Cells/Cationic Liposome Complex/Inducible Nitric Oxide Synthase (iNOS) cDNA/Barath® Intramural Local Drug Delivery Device (Infiltrator®)

Kuntz, Richard E., Brigham and Women's Hospital, Boston, Massachusetts; *Restenosis Gene Therapy Trial - Phase I Study (REGENT I).* Sponsor: Cardion AG

NIH/OBA Receipt Date: 9-20-00. Publicly Reviewed at the December 2000 RAC meeting
Closed: 10-01

0009-412 (Open) Gene Therapy/Phase III/Cancer/Squamous Cell Carcinoma of the Head and Neck (SCCHN)/Tumor Suppressor Gene/In Vivo/Adenovirus Serotype 5/p53 cDNA/Intratumoral Injections [INGN 201 (Ad5CMV-p53)-T302]

Haigentz, Missak, Montefiore Medical Center, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York; Nemunaitis, John J., Mary Crowley Medical Research Center, Dallas, Texas; Hamm, John T, Louisville Oncology, Norton Healthcare, Inc., Louisville, Kentucky; Spiro, Jeffrey, University of Connecticut Health Center, Farmington, Connecticut; Van Echo, David, University of Maryland, Baltimore, Maryland; Yoo, George, Wayne State University, Detroit, Michigan; Cobb, Patrick, Billings Oncology Associates, Billings, Montana; Brockstein, Bruce, Evanston Hospital, Evanston, Illinois; Flood, William, The Milton S. Hershey Medical Center, Hershey, Pennsylvania; Krempl, Greg, University Hospital, Oklahoma City, Oklahoma; Goodwin, W. Jarrard, University of Miami Hospital and Clinics, Miami, Florida; Trask, Douglas, University of Iowa Hospitals and Clinics, Iowa City, Iowa; Zitsch, Robert, University of Missouri Health Care, Columbia, Missouri; Breau, Randall, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Cullen, Kevin, Georgetown University Medical Center, Washington, D.C.; Hrushesky, William, J. M., Dorn Veterans Affairs Medical Center, Columbia, South Carolina; Clayman, Gary, University of Texas, MD Anderson Cancer Center, Houston, Texas; Nemechek, Andrew, Tulane Cancer Center, New Orleans, Louisiana; Guthrie, Troy H., Jr., University of Florida, Jacksonville, Florida; Trask, Douglas, University of Iowa Health Care, Iowa City, Iowa; Arquette, Matthew, Washington University School of Medicine, St. Louis, Missouri; and Villaret, Douglas, University of Florida, Gainesville, Florida; *A Phase III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intratumoral Administration of INGN 201 in Combination with Chemotherapy Versus Chemotherapy Alone in 288 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Aventis Pharmaceuticals - Gencell Division

NIH/OBA Receipt Date: 9-22-00. Not Selected for RAC Public Review: 10-13-00

0009-413 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Naked Plasmid/Tyrosinase cDNA/Intra-lymphnodal Injection

Weber, Jeffrey, Keck/USC School of Medicine, USC Norris Center and Hospital, Los Angeles, California; Smith II, John W., Earl A. Chiles Research Institute Providence Portland Medical Center, Portland, Oregon; and Johnson, Denise, Stanford University, Stanford, California; *A Phase I Dose Ranging Safety Study Using Intra-Nodal Delivery of a Plasmid DNA (Synchrotope TA2M) in Adult Stage IV Melanoma Patients.*

NIH/OBA Receipt Date: 9-29-00. Not Selected for RAC Public Review: 11-7-00
Study complete: 4-4-02

0010-414 (Open) Gene Therapy/Phase I-II/Cancer/Hepatocellular Carcinoma/In Vitro/Autologous Dendritic Cells/Adenovirus/Alpha Fetoprotein/Intravenous Infusion

Economou, James S., Glapsy, John A., and McBride, William H., UCLA Medical Center, Los Angeles, California; *A Phase I/II Trial Testing Alpha-Fetoprotein (AFP) Genetic Immunization in Hepatocellular Carcinoma.*

NIH/OBA Receipt Date: 10-2-00. Not Selected for RAC Public Review: 10-23-00

0010-415 (Open) Gene Therapy/Phase II/Cancer/Ovarian/Oncogene-Regulation/In Vivo/Cationic Liposome Complex/DC-Chl-DOPE/E1A/Intraperitoneal Administration

Ueno, Naoto, University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase II Study of Intraperitoneal E1A-Lipid Complex for Patients with Advanced Epithelial Ovarian Cancer without HER-2/neu Overexpression.* Sponsor: Targeted Genetics Corporation

NIH/OBA Receipt Date: 10-6-00. Not Selected for RAC Public Review: 11-2-00

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0010-416 (Open) Gene Therapy/Phase II/Cancer/Ovarian/Oncogene-Regulation/In Vivo/Cationic Liposome Complex/DC-Chl-DOPE/E1A/Intraperitoneal Administration

Ueno, Naoto, University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase II Study of Intraperitoneal E1A-Lipid Complex for Patients with Advanced Epithelial Ovarian Cancer with HER-2/neu Overexpression.* Sponsor: Targeted Genetics Corporation

NIH/OBA Receipt Date: 10-6-00. Not Selected for RAC Public Review: 11-2-00

0010-417 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Colorectal/Hepatic Metastasis/Dominant Negative Mutation/In Vivo/Retrovirus/dnG1 Cyclin/Hepatic Arterial Infusion

Lenz, Heinz-Josef, Norris Cancer Center, University of Southern California, Los Angeles, California; *Tumor Site Specific Phase I/II Evaluation of Safety and Efficacy of Hepatic Arterial Infusion of a Matrix-Targeted Retroviral Vector Bearing a Dominant Negative Cyclin G1 (dnG1) Construct as Treatment for Colorectal Carcinoma Metastatic to Liver.*

NIH/OBA Receipt Date: 10-13-00. Publicly Reviewed at the December 2000 RAC meeting

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0010-418 (Open) Gene Therapy/Phase II/Cancer/Prostate/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Percutaneous Transperineal Intraprostatic Injection

Pollack, Alan, The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Randomized Phase II Study of Ad5CMV-p53 plus Radioactive Seed Implant vs Seed Implant Alone for PSA Relapse after External Beam Radiotherapy for Prostate Cancer.* Sponsor: Introgen Therapeutics, Inc.

NIH/OBA Receipt Date: 10-16-00. Not Selected for RAC Public Review: 11-7-00

0010-419 (RAC Reviewed with Recommendations) Gene Therapy/Cancer/Melanoma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/fhVII/hFc cDNA/Intratumoral Injection

Deisseroth, Albert, Yale University School of Medicine, New Haven Connecticut; *Intratumoral Injections of a Replication-Incompetent Adenoviral Vector Encoding a Factor VII Immunoconjugate to Induce a Cytolytic Immune Response against Melanoma Tumors: A Pilot Trial.*

NIH/OBA Receipt Date: 10-18-00. Publicly Reviewed at the December 2000 RAC meeting

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0010-420 (Open) Gene Therapy/Phase I-II/Other Disorders/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Crystal, Ronald G, Cornell University Medical College, New York, New York; and Rosengart, Todd, Evanston Northwestern Healthcare, Evanston, Illinois; *Phase I/II, Prospective, Placebo Controlled, Randomized Assessment of Direct Administration of a Replication Deficient Adenovirus Vector ($Ad_{CU}VEGF121.1$) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease as an Adjunct to Coronary Bypass Surgery.*

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-421 (Open) Gene Therapy/Phase I/Other Disorders/Ulcer/In Vivo/Adenovirus/Serotype 5/Platelet Derived Growth Factor (PDGF) cDNA/Intra Ulcer Administration

Mozingo, David, University of Florida College of Medicine, Gainesville, Florida; *A Dose Escalating Phase I Study of AdPDGF-B/GAM in the Treatment of Diabetic Ulcers of the Lower Extremity.* Sponsor: Selective Genetics, Inc.

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-422 (Open) Gene Therapy/Phase I/Infectious Diseases/HIV-1/Replication Inhibition/Single Chain Antibody Gene/In Vitro/Autologous Peripheral Blood Lymphocytes/Retrovirus/sFvhutat2 ant-HIV-1 Tat Protein Antibody/Intravenous Infusion

Marasco, Wayne, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Pilot Study to Evaluate the Safety and Effects of Autologous Lymphocytes Transduced with a Human Single-Chain Antibody Directed against the HIV-1 Tat Protein in HIV-1 Infected Human Subjects with Advanced Disease.*

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-423 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Monogenic Diseases/Junctional Epidermolysis Bullosa/In Vitro/Autologous Keratinocytes/Retrovirus/Laminin 5-beta3 cDNA/Skin Graft

Kimball, Alexa B., Stanford University Medical Center; *Laminin 5 Beta 3 Gene Therapy for Junctional Epidermolysis Bullosa.*

NIH/OBA Receipt Date: 10-18-00. Publicly Reviewed at the December 2000 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0010-424 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Muscle Cells/Plasmid DNA/Poloxamer 188/Del-1 cDNA/ Intramuscular Injection

Hinohara, Tomoaki, Cardiovascular Medicine and Coronary Interventions, Redwood City, California; Litt, Marc R., Jacksonville Heart Center, Jacksonville, Florida; Karlsberg, Ronald P., Cardiovascular Research Institute, Beverly Hills, California; Schaer, Gary L., Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; Piana, Robert, Vanderbilt University Medical Center, Nashville, Tennessee; and Jaff, Michael, The Heart and Vascular Institute of New Jersey, Morristown, New Jersey; *Developmentally Regulated Endothelial Locus (Del-1) Gene Medicine (VLTS-589) A Phase I Multi-Center, Open-Label, Single-Dose Escalation Clinical Safety Trial of VLTS-589 for the Treatment of Patients with Peripheral Arterial Disease.* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-425 (Under Review) Gene Therapy/Phase I/Other Disorders/Bone Fracture/In Vivo/Plasmid DNA/Collagen Sponge/Parathyroid Hormone cDNA/Bone Administration

Goulet, James Alan, University of Michigan; *A Prospective, Randomized Study to Assess the Safety of MAT-100 in Open Tibia Fractures Requiring an Intramedullary Rod (Phase I).* Sponsor: EBI, L.P./Biomed, Inc. and Selective Genetics, Inc.

NIH/OBA Receipt Date: 10-18-00. Review at a RAC meeting pending; sponsor has requested postponement of public review.

0010-426 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/In Vivo/Adenovirus Serotype 5/Replication-Competent Virus/Osteocalcin Promoter/Intratumoral Injection

Gardner, Thomas A., Indiana School of Medicine, Indianapolis, Indiana; *A Phase I Study of Intratumoral Injections of OCaP1 for Metastatic or Locally Recurrent Prostate Cancer, Part 1: Dose Finding, Part 2: Index Lesion Escalation.* Sponsor: DirectGene, Inc.

NIH/OBA Receipt Date: 10-18-00. Publicly Reviewed at the December 2000 RAC meeting

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0010-427 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Adenovirus Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intradermal Administration

Crystal, Ronald G., Cornell University Medical College, New York, New York; *Effect of $Ad_{GV}CFTR.10$ on the Cystic Fibrosis Phenotype.*

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-428 (Open) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/Pro-Drug/In Vivo/Adenovirus Serotype 5/Replication-Competent Virus/Cytosine Deaminase cDNA/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Kim, Jae Ho and Freytag, Svend, Henry Ford Health System, Detroit, Michigan; *Phase I Study of Intraprostatic Administration of a Replication-Competent, Oncolytic Adenovirus Using Various Vector formulations to Patients with Localized Prostate Cancer Prior to Radical Prostatectomy.*

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-429 (Open) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell Carcinoma (SCCHN)/Immunotherapy/In Vivo/Fowlpox Virus/B7.1 (CD 80)/ICAM-1/LFA-3/Intratumoral Injection

Van Waes, Carter, National Institutes of Health, Bethesda, Maryland; *Phase I/Pilot Study of Intralesional Immunotherapy with a Recombinant Avipox Virus Engineered to Express a Triad of Co-stimulatory Molecules in Patients with Advanced Squamous Cell Carcinoma of the Head and Neck.*

NIH/OBA Receipt Date: 10-26-00. Not Selected for RAC Public Review: 5-10-01

0011-430 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/Serotype-5/Interleukin-7 cDNA/Intratumoral Injection

Dubinett, Steven M., UCLA School of Medicine, Los Angeles, California; *A Phase I/II Trial Evaluating Intratumoral Injection of Interleukin-7 Gene Modified Autologous Dendritic Cells for the Treatment of Non-Small Cell Lung Cancer.*

NIH/OBA Receipt Date: 11-1-00. Not Selected for RAC Public Review: 11-22-00

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0011-431 (Open) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral Injection

Gonzalez, Rene, University of Colorado Health Sciences Center; and Whitman, Eric D., Missouri Baptist Medical Center; The Melanoma Center of St. Louis, St. Louis, Missouri; Amatruda, Thomas, North Memorial Health Care/Hubert H. Humphrey Cancer Center, Robbinsdale, Minnesota; Morse, Michael, Duke University Medical Center, Durham, North Carolina; Atkins, Michael B., Beth Israel Deaconess Medical Center, Boston, Massachusetts; Bedikian, Agop Y., The University of Texas, MD Anderson Cancer Center, Houston, Texas; Lutzky, Jose, Mt. Sinai Comprehensive Cancer Center, Miami, Florida; Hutchins, Laura, University of Arkansas for Medical Sciences and Central Arkansas Veteran's Healthcare System, Little Rock, Arkansas; Schwarzenberger, Paul, Louisiana State University Health Sciences Center Lions Clinic, and the Medical Center of Louisiana at New Orleans, New Orleans, Louisiana; Patel, Ravi Comprehensive Blood and Cancer Center, Bakersfield, California; Thant, Myo, Maryland Hematology/Oncology Associates, Baltimore, Maryland; Thompson John A., University of Washington Medical Center and the Seattle Cancer Care Alliance, Seattle Washington; Galanis, Evanthia, Mayo Clinic, Rochester, Minnesota; Ernstoff, Marc, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Richards, Jon M., Oncology Specialities, S. C., Park Ridge, Illinois; Klencke, Barbara, University of California, San Francisco Comprehensive Cancer Center at Mount Zion, San Francisco, California; Hersh, Evan M., Arizona Cancer Center, Tucson, Arizona; and Blum, Ronald, Beth Israel Medical Center, New York, New York; *A Phase II Study of High-Dose Allovectin-7 in Patients with Advanced Metastatic Melanoma.* Sponsor: Vical Inc.

NIH/OBA Receipt Date: 11-16-00. Not Selected for RAC Public Review: 12-7-00

0011-432 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE.Vical-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral Injection

Gleich, Lyon, University of Cincinnati Medical Center, Cincinnati, Ohio; Khan, Mumtaz, Henry Ford Health System, Detroit, Michigan; Wolf, Gregory T., University of Michigan Health System, Ann Arbor, Michigan; Stenson, Kerstin M., The University of Chicago, Chicago, Illinois; Weinstein, Gregory, The Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; Lavertu, Pierre, Case Western University, University Hospitals of Cleveland, Cleveland, Ohio; Carroll, William, University of Alabama-Birmingham, Birmingham, Alabama; Hanna, Ehab, University of Arkansas for Medical Sciences, Little Rock, Arkansas; McCaffrey, Thomas, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; and Friedlander, Paul, Louisiana State University Health Sciences Center, New Orleans, Louisiana; *A Phase II Study of Safety and Efficacy of Allovectin-7 Immunotherapy for the Treatment of Primary Resectable Squamous Cell Carcinoma of the Oral Cavity or Oropharynx.* Sponsor: Vical Inc.

NIH/OBA Receipt Date: 11-16-00. Not Selected for RAC Public Review: 12-7-00

0011-433 (Open) Gene Marking/Cancer/Acute or Chronic Myelogenous Leukemia, Non-Hodgkin's Lymphoma, Myelodysplastic Syndrome/In Vitro/Epstein-Barr Virus Specific Allogeneic Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplantation

Brenner, Malcolm, Baylor College of Medicine, Houston, Texas; *A Phase I Trial Evaluating the Use of RFT5-dgA to Deplete Alloreactive Cells Prior to Haploidentical Stem Cell Transplantation.*

NIH/OBA Receipt Date: 11-27-00. Not Selected for RAC Public Review: 12-15-00

0011-434 (Open) Gene Therapy/Phase I/Cancer/Various Types/Immunotherapy/In Vitro/Allogeneic Fibroblasts/Lethally Irradiated/Plasmid DNA/Interleukin-2 cDNA/Intratumoral Injection

Sobol, Robert E., Sidney Kimmel Cancer Center, San Diego, California; *A Phase I Study of Intra-Tumoral Injection with Allogeneic Fibroblasts Genetically Modified to Secrete IL-2 in Patients with Cancer Who Have Failed Standard Therapy*

NIH/OBA Receipt Date: 11-27-00. Not Selected for RAC Public Review: 12-22-00

0011-435 (Open) Gene Therapy/Phase I-II/Cancer/Myeloma/Immunotherapy/In Vitro/Allogeneic K562 Cells/Combination with Untransduced Tumor Cells/Plasmid DNA/GM-CSF cDNA/Intradermal Injection

Borrello, Ivan, Johns Hopkins University School of Medicine, Baltimore, Maryland; *Vaccination in Peripheral Stem Cell Transplant Setting for Multiple Myeloma: The Use of Autologous Tumor Cells with an Allogeneic GM-CSF Producing Bystander Cell Line.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 11-29-00. Not Selected for RAC Public Review: 12-28-00

0012-436 (Open) Gene Therapy/Phase I/Cancer/Glioma/Immunotherapy/In Vitro/Autologous Fibroblasts/In Combination with Untransduced Autologous Tumor and Dendritic Cells/Interleukin-4 cDNA/Intradermal Injection

Okada, Hideho, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; *Gene Therapy of Malignant Gliomas: A Pilot Study of Vaccination with Autologous Glioma-Lysate and Dendritic Cells Admixed with IL-4 Transduced Fibroblasts to Elicit an Immune Response.*

NIH/OBA Receipt Date: 12-5-00. Not Selected for RAC Public Review: 12-27-00

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0012-437 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vivo/Adenovirus/Serotype 5/CD40 Ligand cDNA/Intratumoral Injection

Harvey, Ben-Gary and Crystal, Ronald G., New York Presbyterian Hospital-Weill Medical College, Cornell University, New York, New York; *In Vivo Transfer of the CD40 Ligand Gene to Primary Lung Tumors to Activate Dendritic Cells and Induce Anti-Tumor Immunity.*

NIH/OBA Receipt Date: 12-7-00. Not Selected for RAC Public Review: 12-28-00

0012-438 (Open) Gene Therapy/Cancer/Head and Neck Squamous Cell Carcinoma/Oncogene Regulation/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intratumoral Injection

Arseneau, James C., Albany Regional Cancer Center, Albany, New York; Berman, Barry S., Cancer Centers of Florida, Orlando, Florida; Anthony, Stephen P., Cancer Care Northwest, Spokane, Washington; Richards, Donald A., Tyler Cancer Center, Tyler, Texas; and Nemunaitis, John and Senzer, Neil, US Oncology, Dallas, Texas; *A Multicenter, Phase II Study of Intratumoral Injections of E1A-Lipid Complex and Re-Irradiation for Treatment of Patients with Recurrent Head and Neck Squamous Cell Carcinoma.* Sponsor: Targeted Genetics

NIH/OBA Receipt Date: 12-22-00. Not Selected for RAC Public Review: 3-2-01

0012-439 (Open) Gene Therapy/Phase I/Other/Peripheral Artery Disease/In Vivo/Ischemic Lower Limb/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Intramuscular Injection

Crystal, Ronald G., Weill Medical College, Cornell University, New York, New York; *Gene Therapy in Conjunction with Operative Bypass Grafting for Severe Peripheral Vascular Ischemia in Individuals with Insulin-Dependent Diabetes.*

NIH/OBA Receipt Date: 12-26-00. Not Selected for RAC Public Review: 1-16-01

0101-440 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Plasmid DNA/Murine gp75 Melanoma Antigen/Intramuscular Injection

Wolchok, Jedd D., Memorial Sloan Kettering Cancer Center, New York, New York; *Phase I Study of gp75 DNA Vaccine in Patients with AJCC Stage III and IV Melanoma.* Sponsor: ImClone Systems, Inc.

NIH/OBA Receipt Date: 1-3-01. Not Selected for RAC Public Review: 1-24-01

0101-441 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Vaccinia Virus/B7.1 (CD80)/ICAM-1/LFA-3/Intratumoral Injection

Kaufman, Howard L., Columbia University, New York, New York; *A Phase I Trial of Intralesional rV-TRICOM Vaccine in the Treatment of Malignant Melanoma.*

NIH/OBA Receipt Date: 1-4-01. Not Selected for RAC Public Review: 1-26-01

0101-442 (Open) Gene Therapy/Phase I-II/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Crystal, Ronald G., Weill Medical College, Cornell University, New York, New York; and Rosengart, Todd K., Evanston Northwestern Healthcare, Evanston, Illinois; *Phase I/II, Prospective Placebo Controlled, Randomized Assessment of Adenoviral Mediated VEGF121 cDNA Myocardial Angiogenesis Therapy as an Adjunct to Individuals with Diffuse Coronary Artery Disease Undergoing Off-Pump Coronary Artery Bypass Surgery.*

NIH/OBA Receipt Date: 1-9-01. Not Selected for RAC Public Review: 1-30-01

0101-443 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/Antisense TAR/Antisense tat-rev/In Vitro/CD34+ Cells/Intravenous

Laurence, Jeffrey C., Cornell University Medical College, New York, New York; *Evaluation of the Safety and Effects of ex vivo Modification and Re-Infusion of CD34+ Cells by an Antisense Construct Against HIV-1 in a Retrovirus Vector.* Sponsor: Enzo Therapeutics, Inc.

NIH/OBA Receipt Date: 1-10-01. Publicly Reviewed at the March 2001 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0101-444 (Open) Gene Therapy/Phase I/Coronary Artery Disease/In Vivo/Muscle Cells/Plasmid DNA/Poloxamer 188/Del-1 cDNA/ Retrograde Intravenous (rIV) Injection into the Heart

Dreiling, Roger J., Cardiovascular Consultants of Oregon, Corvallis, Oregon; *A Phase I Multi-Center, Open-Label, Single-Dose Escalation Clinical Trial of VLTS-589 for Treatment of Patients with Coronary Artery Disease*. Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 4-20-01

0101-445 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Clayman, Gary, The University of Texas MD Anderson Cancer Center, Houston, Texas; *Clinical Protocol for Wild Type p53 Gene Induction in Premalignancies of Squamous Epithelium of the Oral Cavity Via an Adenoviral Vector.* Sponsor: Introgen Therapeutics, Inc.

NIH/OBA Receipt Date: 1-10-01. Publicly Reviewed at the March 2001 RAC meeting

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0101-446 (Open) Gene Therapy/Phase I/Monogenic Disease/Severe Combined Immune Deficiency Due to JAK3 Deficiency/In Vitro/Autologous CD34+ Cells from Peripheral Blood or Bone Marrow/Retrovirus/JAK3 cDNA/Intravenous Infusion

Sorrentino, Brian P. and Cunningham, John M., St. Jude Children's Research Hospital, Memphis, Tennessee; and Buckley, Rebecca, Duke University School of Medicine, Durham, North Carolina; *Transplantation of Gene-Corrected Autologous CD34+ Hematopoietic Stem Cells in Previously Transplanted Patients with JAK3 Deficiency and Persistent Humoral Immune Defects.*

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-447 (Open) Gene Therapy/Phase I/Cancer/Prostate Cancer/In Vivo/Dendritic Cells/Adenovirus/Serotype 5/PSA cDNA/Subcutaneous Injection

Lubaroff, David, University of Iowa, Iowa City, Iowa; *Phase I Study of Adenovirus/PSA Vaccine in Men with Metastatic Prostate Cancer.*

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-448 (Open) Gene Therapy/Phase II-III/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Swisher, Stephen, University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase II/III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intralesional Administration of RPR/INGN 201 in Combination with Taxotere® and Carboplatin and Radiotherapy Versus Taxotere® and Carboplatin and Radiotherapy Alone in Patients with Locally Advanced Unresectable Non-Small Cell Lung Cancer (NSCLC).* Sponsor: Introgen Therapeutics, Inc.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-449 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Interleukin-12 cDNA/Intratumoral Injection

Miles, Brian J., Baylor College of Medicine, Houston, Texas; *Phase I Study of Adenoviral Vector Delivery of the IL-12 Gene in Men with Local Recurrence of Prostate Cancer After Irradiation Therapy.*

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-450 (Open) Gene Therapy/Phase II/Cancer/Prostate Cancer/Vector Directed Cell Lysis/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Replication Competent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen/Intratumoral Injection

DeWeese, Theodore, Johns Hopkins Oncology Center, Baltimore, Maryland; Roach III, Mack, University of California, San Francisco, San Francisco, California; and Michalski, Jeff, Washington University Medical School, Saint Louis, Missouri; *A Phase II Randomized Comparison Study of an Intraprostatic Injection of CV7606 Followed by External Beam Radiotherapy (EBRT) Versus EBRT Alone in Patients with Intermediate Risk, Clinically Localized Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0101-451 (Open) Gene Therapy/Phase II/Cancer/Prostate/Vector Directed Cell Lysis/In Vivo/Adenovirus/Serotype 5/Replication Competent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen/Intravenous Injection

Small, Eric, University of California, San Francisco, San Francisco, California; *A Randomized, Placebo Controlled Phase II Study of an Intravenous Injection of CV787, a Prostate-Specific Antigen Oncolytic Adenovirus, Plus Weekly Docetaxel in Patients with Metastatic Hormone Refractory Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-452 (Open) Gene Therapy/Phase IIb-III/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Fibroblast Growth Factor (FGF) cDNA/Intracoronary Administration

Grines, Cindy L., William Baumont Hospital, Royal Oak, Michigan; Bethala, Vasanth, Medical Research Institute, Slidell, LA; Erenrich, Norman, Florida Cardiovascular Research, Atlantis, FL; Gammon, Roger, Austin Heart, Austin, TX; Henry, Timothy, Abbott Northwestern Hospital, Minneapolis, MN; Licandro, Rudolph, Louisville Cardiology Medical Group, Louisville, KY; Saucedo, Jorge, University of Arkansas for Medical Sciences, Little Rock, AR; Tonkon, Melvin, Anaheim Heart and Research Institute, Santa Ana, CA; Watkins, Matthew , The University of Vermont, Burlington, VT; Grossman, P. Michael, The University of Michigan Health System, Ann Arbor, Michigan; Butman, Samuel, University Medical Center, University of Arizona, Tucson, Arizona; Churchill, David A., Washington Regional Medical Center, Fayetteville, Arkansas; Conn, Eric H., The Chattanooga Heart Institute, Chattanooga, Tennessee; Coppola, John T., Saint Vincent Catholic Medical Centers of New York, New York, New York; Fuchs, Shmuel, Washington Hospital Center, Washington, D.C.; Ghali, Jalal K., Cardiac Centers of Louisiana, Shreveport, Louisiana; Hodes, Zachary I., The Care Group, LLC, Indianapolis, Indiana; Nadar, Venkatesh K., Heritage Cardiology Associates, Camp Hill, Pennsylvania; Rowe, Steven K., Heartland Regional Medical Center, St. Joseph, Missouri; Brennan, Theresa, University of Iowa Healthcare, Iowa City, Iowa; Browne, Jr., Kevin F., Watson Clinic LLP, Lakeland, Florida; Dib, Nabil, Arizona Heart Institute, Phoenix, Arizona; Ellis, Stephen, Cleveland Clinic Foundation, Cleveland, Ohio; Hart, Kevin, Stucky Research Center, Fort Wayne, Indiana; Iskandrian, Ami E., University of Alabama at Birmingham, Birmingham, Alabama; Kleiman, Neal S., Baylor College of Medicine, Houston, Texas; Marmur, Jonathan, Mount Sinai Hospital, New York, New York; Marshall, J. Jeffrey, Crawford Long Hospital, Atlanta, Georgia; Penny, William F., San Diego VA Medical Center, San Diego, California; Pepine, Carl J., University of Florida, Gainesville, Florida; Saenz, Carlos and Taussig, Andrew, Florida Hospital, Orlando, Florida; Schaer, Gary L., Rush-Presbyterian St. Luke's Medical Center, Chicago, Illinois; Sequeira, Rafael F., University of Miami-Jackson Memorial Hospital, Miami, Florida; Baran, Kenneth W., United's John Nasseff Heart Hospital, Saint Paul, Minnesota; Helmer, Gregory A., Minnesota Heart Clinic, P.A., Edina, Minnesota; Mendelsohn, Farrell O., Cardiology, P.C., Birmingham, Alabama; Moran, John F., Loyola University Medical Center, Maywood, Illinois; Sanborn, Timothy, Evanston Northwestern Healthcare, Evanston, Illinois; Sharaf, Barry L., Rhode Island Hospital, Providence, Rhode Island; Moreyra, Abel E., Robert Wood Johnson Medical School, New Brunswick, New Jersey; Cohen, Eric, Cardiovascular Associates, P.C., Birmingham, Alabama; Lee, Joon, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Levine, Glenn, Houston VA Medical Center, Houston, Texas; Lopez, John, University of Chicago Medical Center, Chicago, Illinois; McGrew, Frank, III, The Stern Cardiovascular Center, Memphis, Tennessee; Thai, Hoang, Southern Arizona Veterans Affairs Health Care System, Tucson, Arizona; Zabalgotia, Miguel, The University of Texas Health Science Center at San Antonio; San Antonio, Texas; Laham, Roger, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Murphy, Patrick, L., The Heart Group, PC, Mobile, Alabama; Rade, Jeffrey J., Johns Hopkins University School of Medicine, Baltimore, Maryland; Simari, Robert D., Mayo Clinic, Rochester, Minnesota; Savage, Michael P., Jefferson Heart Institute, Philadelphia, Pennsylvania; Zoble, Robert G., James A. Haley Veterans Hospital, Tampa, Florida; Kellett, Mirle, Maine Medical Center, Portland, Maine; Moreyra, Abel, Robert Wood Johnson University Hospital, New Brunswick, New Jersey; Niles, Nathaniel, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Ohman, Erik, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and Murray, Conrad, Global Cardiovascular Associates, Inc., Las Vegas, Nevada; *A Multicenter, Randomized, Double-Blind, Placebo Controlled, Dose-Response Study to Evaluate the Efficacy and Safety of Ad5.1FGF-4 in Patients with Stable Angina.* Sponsor: Berlex Laboratories.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-453 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Human Interferon-beta cDNA/Stereotactic Injection

Eck, Stephen L., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Rosenfeld, Steven S., University of Alabama at Birmingham, Birmingham, Alabama; Chiocca, E. Antonio, Massachusetts General Hospital, Boston, Massachusetts; Hamilton, Allan, University of Arizona, Tucson, Arizona; and Lillehei, Kevin, University of Colorado Health Sciences Center, Denver, Colorado; *A Multi-Center, Open Label, Two Part, Dose Escalation Study to Determine the Tolerability of Interferon-beta Gene Transfer in the Treatment of Recurrent or Progressive Glioblastoma Multiforme.* Sponsor: Biogen.

NIH/OBA Receipt Date: 1-12-01. Not Selected for RAC Public Review: 1-31-01

0101-454 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Yoo, George H., Wayne State University, Detroit, Michigan; *Phase II Trial of Surgery with Perioperative RPR/INGN 201 (Ad5CMV-p53) Gene Therapy Followed by Chemoradiotherapy for Advanced Resectable Squamous Cell Carcinoma of the Oral Cavity and Oropharynx.* Sponsor: Southwest Oncology Group.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

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0101-455 (Open) Gene Therapy/Phase II/Cancer/Breast/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Cristofanilli, Massimo, The University of Texas MD Anderson Cancer Center, Houston, Texas; *Phase II, Single Arm, Single Institution Clinical Trial of Docetaxel and Doxorubicin in Combination with Local Administration of Ad5CMV-p53 (RPR/INGN-201) in Locally Advanced Breast Cancer (LABC).* Sponsor: Introgen Therapeutics, Inc.

NIH/OBA Receipt Date: 1-16-01. Not Selected for RAC Public Review: 1-31-01

0101-456 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vivo/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD 80)/ICAM-1/LFA-3/GM-CSF/Intramuscular or Intradermal Injection

von Mehren, Margaret, Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I Study of a Recombinant Fowlpox Vaccine rF-CEA(6D)/TRICOM alone or with GM-CSF in Patients with Advanced CEA Expressing Adenocarcinoma.*

NIH/OBA Receipt Date: 1-25-01. Not Selected for RAC Public Review: 2-27-01

0101-457 (Open) Gene Therapy/Phase I/Cancer/Soft Tissue Sarcoma/In Vivo/Adenovirus/Type 5/Tumor Necrosis Factor cDNA/Intratumoral Injection

Hanna, Nader, University of Kentucky Chandler Medical Center, Lexington, Kentucky; Nemunaitis, John, US Oncology, Dallas, Texas; Sandler, Alan B., Vanderbilt University, Nashville, Tennessee; Vijayakumar, Srinivasan and Warso, Michael, University of Illinois at Chicago, Chicago, Illinois; Mundt, Arno, University of Chicago, Chicago, Illinois; and Richards, Donald A., Tyler Cancer Center, Tyler, Texas; *An Open-Label, Phase I, Dose-Escalation Study of TNFerade™ Biologic with Radiation Therapy as an Adjunct to Surgery or for Palliation of Soft Tissue Sarcoma of the Extremities.* Sponsor: GenVec.

NIH/OBA Receipt Date: 1-29-01. Not Selected for RAC Public Review: 2-26-01

0102-458 (Open) Gene Therapy/Phase II/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vivo/Canarypox Virus/Carcinoembryonic Antigen/B 7.1 (CD80)/Intramuscular and Intradermal Injections

Kaufman, Howard L., Columbia University, New York, New York; von Mehren, Margaret, Fox Chase Cancer Center, Philadelphia, Pennsylvania; Conry, Robert M., The University of Alabama at Birmingham, Birmingham, Alabama; Marshall, John, Georgetown University Medical Center, Washington D.C.; Heim, William J., Hematology & Oncology Associates of Northeastern PA, Dunmore, Pennsylvania; Lenz, Heinz-Josef, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California; Kindler, Hedy, The University of Chicago, Chicago, Illinois; Garrett, Christopher, H. Lee Moffitt Cancer Center, Tampa, Florida; and Urba, Walter, Providence Portland Medical Center, Portland, Oregon; *Pilot Phase II Study of Safety and Immunogenicity of a ALVAC-CEA/B7.1 Vaccine Administered with Chemotherapy, Alone or in Combination with Tetanus Toxoid, as Compared to Chemotherapy Alone, in Patients with Metastatic Colorectal Adenocarcinoma.* Sponsor: Aventis Pasteur Limited.

NIH/OBA Receipt Date: 2-15-01. Not Selected for RAC Public Review: 4-12-01

0103-459 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Adeno-Associated Virus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Corman, John M., Virginia Mason Medical Center, Seattle, Washington; *A Phase I Dose Escalation Study of Human GM-CSF Gene Transduced Irradiated Allogeneic Prostate Cancer Cell Vaccine (GVAX® Prostate Cancer Vaccine (PC-3)) in Patients with Hormone-Refractory Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 3-6-01. Not Selected for RAC Public Review: 7-27-01

0103-460 (Open) Gene Therapy/Phase I/Cancer/Chronic Lymphocytic Leukemia/Non-Hodgkin's Lymphoma/Immunotherapy/In Vitro/Autologous Lymphoma Cells/Adenovirus/Serotype 5/Interleukin-2 cDNA/CD40 Ligand cDNA/Subcutaneous Injection

Takahashi, Satoshi and Brenner, Malcolm, Baylor College of Medicine, Houston, Texas; *Treatment of Chronic Lymphocytic Leukemia (CLL) with IL-2 Gene Modified and Human CD40 Ligand-Expressing Autologous Tumor Cells.*

NIH/OBA Receipt Date: 3-19-01. Not Selected for RAC Public Review: 4-6-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0104-461 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vivo/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Interferon-alpha/Interleukin-12 cDNA/Intratumoral Injection

Posner, Marshall R., Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I/II Multi-Center, Open-Label, Multiple Administration Trial of the Safety, Tolerability, and Efficacy of an IFN-alpha/IL-12 Plasmid-Based Therapeutic.* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 4-9-01. Not Selected for RAC Public Review: 4-27-01

0104-462 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Pro-Drug/In Vivo/Tumor Cells/Salmonella typhimurium/E. coli Cytosine Deaminase cDNA/Intratumoral Injection/Combined with 5fluorocytosine

Nemunaitis, John J. and Cunningham, Charles, Mary Crowley Medical Research Center (US Oncology), Dallas, Texas; *A Phase I Trial of Genetically Modified Salmonella typhimurium Expressing Cytosine Deaminase (TAPET-CD, VNP20029) Administered by Intra-Tumoral Injection in Combination with 5-fluorocytosine for Patients with Advanced or Metastatic Cancer.* Sponsor: Vion Pharmaceuticals, Inc.

NIH/OBA Receipt Date: 4-16-01. Publicly Reviewed at the June 2001 RAC meeting.

0104-463 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Fibroblast Growth Factor 1 cDNA/Intramuscular Injection

Comerota, Anthony J., Temple University School of Medicine, Philadelphia, Pennsylvania; Henry, Tim, Hennepin County Medical Center, Minneapolis, Minnesota; and Chronos, Nicolas, Atlanta Cardiovascular Research Institute, Atlanta, Georgia; *Phase I Double Blind, Parallel-Group, Multi-Center, Gene Expression (Synthesis of FGF-1 mRNA), Safety and Tolerability Study of Increasing Single Doses of NV1FGF Administered by Intra-Muscular Injection in Patients with Severe Peripheral Artery Occlusive Disease (PAOD) Planned to Undergo Amputation Above the Ankle.* Sponsor: Aventis Pharma Recherche-Developpement.

NIH/OBA Receipt Date: 4-16-01. Not Selected for RAC Public Review: 5-4-01

0104-464 (Open) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/Replication-Competent Virus/Pro-Drug/In Vivo/Adenovirus/E. coli Cytosine Deaminase cDNA/5-Fluorocytosine/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Kim, Jae Ho and Freytag, Svend O., Henry Ford Health System, Detroit, Michigan; *Phase I Study of Combined Suicide Gene Therapy and Radiation Therapy for Locally Advanced Carcinoma of the Prostate.*

NIH/OBA Receipt Date: 4-17-01. Not Selected for RAC Public Review: 5-7-01

0104-465 (Open) Gene Therapy/Phase I/Monogenic Disease/Alpha-1 Antitrypsin Deficiency/In Vivo/Adeno-Associated Virus/Alpha-1 Antitrypsin cDNA/Intramuscular Injection

Flotte, Terence R., University of Florida, Gainesville, Florida; *A Phase I Trial of Intramuscular Injection of a Recombinant Adeno-Associated Virus Alpha-1-Antitrypsin (rAAV-AT) Gene Vector to AAT-Deficient Adults.*

NIH/OBA Receipt Date: 4-18-01. Not Selected for RAC Public Review: 5-8-01

0104-466 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Chemoprotection/In Vivo/Cationic Liposome Complex/Cholesterol/DOTIM/Manganese Super Oxide Dismutase (MnSOD)/Intraesophageal Administration

Belani, Chandra P., University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; *Concurrent Chemotherapy (Paclitaxel and Carboplatin) and Thoracic Radiotherapy with Swallowed Manganese Superoxide Dismutase (MnSOD) Plasmid Liposome (PL) Protection in Patients with Locally Advanced Stage III Non-Small Cell Lung Cancer. A Phase I-II Study.*

NIH/OBA Receipt Date: 4-18-01. Not Selected for RAC Public Review: 5-8-01

0104-467 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Other/Peripheral Neuropathy/In Vivo/Endothelial Cells/Plasmid DNA/$VEGF_{165}$ cDNA/Intramuscular Injection

Isner, Jeffrey, St. Elizabeth's Medical Center, Boston, Massachusetts; *VEGF Gene Transfer for Diabetic Neuropathy.*

NIH/OBA Receipt Date: 4-18-01. Publicly Reviewed at the June 2001 RAC meeting.

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0104-468 (Open) Gene Therapy/Phase I-II/Coronary Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/VEGF$_{165}$ cDNA/Intramyocardial Injection

McCarthy, Patrick, The Cleveland Clinic Foundation, Cleveland, Ohio; *VEGF Gene Transfer to Promote Angiogenesis in Patients with Advanced Heart Failure.*

NIH/OBA Receipt Date: 4-18-01. Not Selected for RAC Public Review: 5-8-01

0104-469 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Other/Parkinson's Disease/In Vivo/Adeno-Associated Virus/Glutamic Acid Decarboxylase 65-67 cDNA/Intracerebral Administration

During, Matthew J., Jefferson Medical College, Philadelphia, Pennsylvania and Kaplitt, Michael, New York Hospital-Weill Medical College of Cornell University, New York, New York; *Subthalamic GAD Gene Transfer in Parkinson Disease Patients Who Are Candidates for Deep Brain Stimulation.*

NIH/OBA Receipt Date: 4-18-01. Publicly Reviewed at the June 2001 RAC meeting.

0104-470 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Osteosarcoma Metastasis to Lung/Vector-Directed Cell Lysis/In Vivo/Adenovirus Serotype 5/Replication-Competent Virus/Promoter of Osteocalcin/Intravenous Injection

Meyers, Paul A., Memorial Sloan-Kettering Cancer Center, New York, New York and Reaman, Gregory H., George Washington University School of Medicine and Children's National Medical Center, Washington, D.C.; *A Phase I/II Dose Escalation and Activity Study of Intravenous Injections of OCaP1 in Subjects with Refractory Osteosarcoma Metastatic to Lung.* Sponsor: DirectGene, Inc.

NIH/OBA Receipt Date: 4-18-01. Publicly Reviewed at the June 2001 RAC meeting.

0104-471 (Open) Gene Therapy/Cancer/Breast Cancer/In Vivo/Tumor Suppressor/Adenovirus/Melanoma Differentiation Associated Protein-7 cDNA/Intratumoral Injection

Buchholz, Thomas A., MD Anderson Cancer Center, Houston, Texas; *A Phase I/II Dose-Escalation Trial of Intratumoral Injection with a Replication-Deficient Adenovirus Vector, Ad-mda7 (INGN 241), in Combination with Radiation Therapy in Patients with Locally Recurrent Breast Cancer.* Sponsor: Introgen Therapeutics, Inc.
NIH/OBA Receipt Date: 4-18-01. Not Selected for RAC Public Review: 5-8-01

0105-472 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vitro/Allogeneic K562 Cells/Combination with Untransduced Tumor Cells/Plasmid DNA/GM-CSF cDNA/Intradermal Injection

Smith II, John W., Providence Portland Medical Center, Portland, Oregon; Aboulafia, David, Virginia Mason Medical Center, Seattle, Washington; Sternman, Daniel H., University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; and Jablons, David M., University of California, San Francisco, San Francisco, California; *Phase I/II Study of Vaccination with Irradiated Autologous Lung Tumor Cells Mixed with a GM-CSF Secreting Bystander Cell Line (Lung Bystander GVAX®) in Advanced Non-Small Cell Lung Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 5-14-01. Not Selected for RAC Public Review: 6-4-01

0105-473 (Open) Gene Marking/Cancer/EBV-Positive Hodgkin Disease/In Vitro/LMP2A-Specific Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Adenovirus/LMP2A cDNA/Intravenous Administration

Gahn, Benedikt, Heslop, Helen, and Rooney, Cliona, Baylor College of Medicine, Houston, Texas; *Administration of Neomycin Resistance Gene Marked LMP2A-Specific Cytotoxic T Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin's Lymphoma.*

NIH/OBA Receipt Date: 5-14-01. Not Selected for RAC Public Review: 6-4-01

0105-474 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Plasmid DNA/Human and Mouse Prostate Specific Membrane Antigen cDNAs/Intramuscular Injection

Scher, Howard I., and Wolchok, Jedd, D., Memorial Sloan-Kettering Cancer Center, New York, New York; *Vaccination of Prostate Cancer Patients with Human and Mouse Specific Membrane Antigen (PSMA) DNA Vaccine: A Pilot Trial to Assess Safety and the Immune Response.*

NIH/OBA Receipt Date: 5-24-01. Not Selected for RAC Public Review: 6-14-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0106-475 (Open) Gene Therapy/Phase II/Cancer/Pancreas/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Plasmid/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Intradermal Injection

Jaffee, Elizabeth M., Johns Hopkins University School of Medicine, Baltimore, Maryland; *A Safety and Efficacy Trial of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene in Combination with Adjuvant Chemotherapy for the Treatment of Adenocarcinoma of the Pancreas.*

NIH/OBA Receipt Date: 6-11-01. Not Selected for RAC Public Review: 6-29-01

0106-476 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) cDNA/Aerosol Administration

Virella-Lowell, Isabel, University of Florida, College of Medicine, Gainesville, Florida; *Evaluation of Anti-Inflammatory and Anti-Protease Pretreatment on the Delivery of Aerosolized tgAAVCF to Cystic Fibrosis Patients with Mild Lung Disease.* Sponsor: Targeted Genetics.

NIH/OBA Receipt Date: 6-11-01. Not Selected for RAC Public Review: 7-12-01

0106-477 (Open) Gene Therapy/Phase I/Cancer/Solid Tumors/Immunotherapy/In Vivo/Fowlpox Virus/B7.1 (CD80)/ICAM-1/LFA-3/Intratumoral Injection

Kaufman, Howard L., Albert Einstein College of Medicine, Bronx, New York; *Intra-Lesional rF-B7.1 Versus rF-TRICOM Vaccine in the Treatment of Metastatic Cancer.*

NIH/OBA Receipt Date: 6-12-01. Not Selected for RAC Public Review: 7-2-01

0106-478 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vitro/Autologous Dendritic Cells/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD80)/ICAM-1/LFA-3/GM-CSF/Intravenous

Lyerly, H. Kim, Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Active Immunotherapy with Autologous Dendritic Cells Infected with CEA-6D Expressing Fowlpox-TRICOM in Patients with Advanced or Metastatic Malignancies Expressing CEA.*

NIH/OBA Receipt Date: 6-28-01. Not Selected for RAC Public Review: 7-19-01

0106-479 (Open) Gene Therapy/Phase I-II/Cancer/Acute Myelogenous Leukemia/Immunotherapy/In Vitro/Allogeneic K562 Cells/Plasmid DNA/GM-CSF cDNA/Intradermal Injection

Borrello, Ivan, Johns Hopkins University School of Medicine, Baltimore, Maryland; Stock, Wendy, University of Chicago, Chicago, Illinois; Damon, Lloyd, University of California, San Francisco, San Francisco, California; and DeAngelo, Daniel, Dana Farber Cancer Institute, Boston, Massachusetts; *Vaccination in Peripheral Stem Cell Transplant Setting for Acute Myelogenous Leukemia: The Use of Autologous Tumor Cells with an Allogeneic GM-CSF Producing Bystander Cell Line.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 6-29-01. Not Selected for RAC Public Review: 7-20-01

0107-480 (RAC Reviewed with Recommendations) Gene Therapy/Phase IIb/Other/End Stage Renal Disease/Stenosis Prevention/In Vivo/Adenovirus/Vascular Endothelial Growth Factor D/Perivascular Collagen Collar Device

Fuster, Valentin, Mount Sinai Medical Center, New York, New York; *A Phase IIb, Randomized, Multicenter, Double-Blind Study of the Efficacy and Safety of Trinam™ (EG004) in Stenosis Prevention at the Graft-Vein Anastomosis Site in Dialysis Patients.* Sponsor: Ark Therapeutics, Ltd.

NIH/OBA Receipt Date: 7-6-01. Publicly Reviewed at the September 2001 RAC meeting.

0107-481 (Open) Gene Therapy/Phase Ib-II/Cancer/Brain Tumors/Malignant Glioma/Vector-Directed Cell Lysis/In Vivo/Herpes Simplex Virus Type 1/Tumor Lysis/Intracerebral Injection

Markert, James M., University of Alabama at Birmingham, Birmingham, Alabama; *An Open-Label, Phase Ib/II Study of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally to Subjects with Recurrent Malignant Glioma.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 7-9-01. Not Selected for RAC Public Review: 7-31-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0107-482 (Open) Gene Therapy/Phase Ib-II/Cancer/Brain Tumors/Malignant Glioma/Vector-Directed Cell Lysis/In Vivo/Herpes Simplex Virus Type 1/Tumor Lysis/Intracerebral Injection

Markert, James M., University of Alabama at Birmingham, Birmingham, Alabama; *Long-Term Follow-Up of the Safety and Survival of Subjects with Recurrent Malignant Glioma Who Enrolled in a Phase Ib/II Study (protocol 0107-481) of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 7-9-01. Not Selected for RAC Public Review: 7-31-01

0107-483 (Open) Gene Therapy/Phase Ib-II/Cancer/Brain Tumors/Malignant Glioma/Vector-Directed Cell Lysis/In Vivo/Herpes Simplex Virus Type 1/Tumor Lysis/Intracerebral Injection

Markert, James M., University of Alabama at Birmingham, Birmingham, Alabama; *Long-Term Follow-Up of the Safety and Survival of Subjects with Recurrent Malignant Glioma Who Enrolled in a Phase Ib/II Study (protocol 0107-481) of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 7-9-01. Not Selected for RAC Public Review: 7-31-01

0107-484 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/In Vivo/Plasmid in Poly (DL-lactide-coglycolide) (PLG) Microparticles/Cytochrome P450 isoenzyme 1B1 (CYP1B1) Gene/Intramuscular Injection

Gribben, John G., Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Open-Label Study of the Safety and Feasibility of Vaccinating Cancer Patients with Repeated Doses of ZYC300.* Sponsor: ZYCOS, Inc.

NIH/OBA Receipt Date: 7-11-01. Not Selected for RAC Public Review: 7-31-01

0107-485 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Breast/In Vitro/Autologous Bone Marrow Cells/Adenovirus/bcl-2 Dominant Negative Mutant/Bone Marrow Transplant

Clarke, Michael F., University of Michigan, Ann Arbor, Michigan; *Purging of Autologous Stem Cell Sources with bcl-x_s Adenovirus for Women Undergoing High-Dose Chemotherapy for Stage IV Breast Carcinoma.*

NIH/OBA Receipt Date: 7-11-01. Publicly Reviewed at the September 2001 RAC meeting.

0107-486 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition/In Vitro/Autologous CD34+ Cells/Retrovirus/Hammerhead Ribozyme/Intravenous

Mitsuyasu, Ronald, UCLA Medical Center, Los Angeles, California; and Merigan, Thomas C., Jr., Stanford Medical Center, Stanford, California; *A Randomized Phase II, Double-Blind, Controlled Trial to Evaluate the Safety and Efficacy of Autologous CD34+ Hematopoietic Progenitor Cells Transduced with Either a Delivery Gene Construct (LNL6) or LNL6 that Contains an Anti-HIV-1 Ribozyme in Patients with HIV-1 Infection.* Sponsor: Johnson & Johnson Research Pty Limited.

NIH/OBA Receipt Date: 7-11-01. Not Selected for RAC Public Review: 7-31-01

0107-487 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Other/Age-related Macular Degeneration (AMD)/Adenovirus/Pigment-Epithelium Derived Factor (PEDF) cDNA/Intravitreal Administration

Campochiaro, Peter A., Johns Hopkins University School of Medicine, Baltimore, Maryland; *An Open-Label, Phase I, Single Administration, Dose Escalation Study of $AD_{GV}PEDF.11D$ (ADPEDF) in Neovascular Age-Related Degeneration (AMD).* Sponsor: GenVec, Inc.

NIH/OBA Receipt Date: 7-11-01. Publicly Reviewed at the September 2001 RAC meeting.

0107-488 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Infectious Diseases/Human Immunodeficiency Virus/Replication Inhibition/Antisense/In Vitro/CD4+ Autologous Peripheral Blood Cells/Lentivirus/HIV-1/Antisense env/Intravenous

MacGregor, Rob Roy, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *A Phase I Open-Label Clinical Trial of the Safety and Tolerability of Single Escalating Doses of Autologous CD4 T Cells Transduced with VRX496 in HIV Positive Subjects.* Sponsor: VIRxSYS Corporation.

NIH/OBA Receipt Date: 7-12-01. Publicly Reviewed at the September 2001 RAC meeting.

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0107-489 (Open) Gene Therapy/Phase I/Other/Restenosis In Vivo/Plasmid DNA/Vascular Endothelial Growth Factor cDNA/Intraarterial/Angioplasty Catheter

Losordo, Douglas W., St. Elizabeth's Medical Center, Boston, Massachusetts; *VEGF Gene Transfer to Prevent Coronary Artery Restenosis.*

NIH/OBA Receipt Date: 7-12-01. Not Selected for RAC Public Review: 7-31-01

0107-490 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vivo/Naked Plasmid/Melan-A/MART-1/Intralymphnodal Injection

Weber, Jeffrey S., University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California; Hersh, Evan M., Arizona Cancer Center, Tucson, Arizona; Smith II, John W., Providence Portland Medical Center, Portland, Oregon; and Lerner, Adam, Boston University School of Medicine, Boston, Massachusetts; *A Pilot Phase I/II Study of Intranodal Delivery of a Plasmid DNA (Synchrovax SEM Vaccine) in Stage IV Melanoma Patients.* Sponsor: CTL ImmunoTherapies Corp.

NIH/OBA Receipt Date: 7-19-01. Not Selected for RAC Public Review: 8-8-01.

0107-491 (Open) Gene Therapy/Phase I/Cancer/Follicular Non-Hodgkin's Lymphoma/Immunotherapy/In Vitro/ Autologous T Lymphocytes/Plasmid DNA/Electroporation/CE7R-Specific scFvFc-Zeta T Cell Receptor/Intravenous Infusion

Press, Oliver W., University of Washington Medical Center, Seattle Washington; *A Phase I Study to Evaluate the Safety of Cellular Immunotherapy Using Genetically-Modified Autologous CD20-Specific CD8+ T Cell Clones for Patients with Relapsed CD20+ Indolent Lymphomas.*

NIH/OBA Receipt Date: 7-26-01. Not Selected for RAC Public Review: 8-15-01

0107-492 (Withdrawn-replaced by protocol # 0110-499) Gene Therapy/Phase I/Cancer/Liver (Hepatic) Metastases/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Sung, Max W., Mount Sinai Medical Center, New York, New York; *Clinical Trial of Adenoviral Vector Delivery of the Herpes Thymidine Kinase (HSV-TK) Gene by Intratumoral Injection Followed by Intravenous Ganciclovir with Imaging of HSV1-tk Gene Expression in Patients with Hepatic Metastases from Colorectal Cancer.*

NIH/OBA Receipt Date: 7-27-01.

0107-493 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Adeno-Associated Virus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Corman, John M., Virginia Mason Medical Center, Seattle, Washington; Simons, Jonathan, Emory University, Atlanta, Georgia; Small, Eric, University of California, San Francisco, San Francisco, California; Higano, Celestia, University of Washington, Seattle, Washington; Smith, David, University of Michigan Medical Center, Ann Arbor, Michigan; and Hudes, Gary R., Fox Chase Cancer Center, Philadelphia, Pennsylvania; *A Phase I/II Dose Escalation and Efficacy Trial of GVAX® Prostate Cancer Vaccine in Patients with Metastatic Hormone-Refractory Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 7-18-01. Not Selected for RAC Public Review: 8-31-01

0108-494 (Open) Gene Therapy/Monogenic Disease/X-Linked Severe Combined Immune Deficiency/In Vitro/Autologous CD34+ Cells from Cord Blood or Bone Marrow/Retroviral Vector/γc cDNA/Intravenous Infusion

Weinberg, Kenneth I., Children's Hospital of Los Angeles, University of Southern California School of Medicine, Los Angeles, California; *Gene Transfer of the γcDNA into CD34+ Hematopoietic Cells of Infants or Children with X-Linked Severe Combined Immune Deficiency (X-SCID).*

NIH/OBA Receipt Date: 8-27-01. Not Selected for RAC Public Review: 9-17-01

0108-495 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy/In Vivo/Vaccinia Virus/DF3/MUC1/B7.1 (CD 80)/ICAM-1/LFA-3/Intradermal Injection

Eder, Joseph Paul, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Trial of Recombinant Vaccinia Viruses that Express DF3/MUC1 and TRICOM (B7.1, ICAM-1, and LFA-3) in Patients with Metastatic Adenocarcinoma of the Breast.*

NIH/OBA Receipt Date: 8-27-01. Not Selected for RAC Public Review: 3-6-02

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0108-496 (Open) Gene Therapy/Phase I/Cancer/Malignant Glioma/Immunotherapy/In Vitro/Autologous T Lymphocytes/Plasmid DNA/Electroporation/IL13R α 2-Specific scFvFc-Zeta T Cell Receptor/Intracavity Administration

Jensen, Michael, City of Hope National Medical Center, Duarte, California; *Pilot Feasibility and Safety Study of Cellular Immunotherapy for Recurrent/Refractory Malignant Glioma using Genetically Modified Autologous CD8+ T Cell Clones.*

NIH/OBA Receipt Date: 8-30-01. Not Selected for RAC Public Review: 9-21-01

0109-497 (Open) Gene Therapy/Phase II/Cancer/MUC-1 Expressing Prostate Cancer/Immunotherapy/In Vivo/Vaccinia Virus/MUC-1/Interleukin-2/Subcutaneous Injection

Pantuck, Allan J., University of California, Los Angeles, Los Angeles, California; Dreicer, Robert, Cleveland Clinic Foundation, Cleveland, Ohio; Conlon, Kevin, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; Sahasrabudhe, Deepak, University of Rochester Medical Center, Rochester, New York; Higano, Celestia, Seattle Cancer Care Alliance, Seattle, Washington; Ahmann, Frederick, University of Arizona Cancer Center, Tucson, Arizona; and Stadler, Walter, University of Chicago, Chicago, Illinois; *Randomized Multicenter Phase II Study Evaluating Two Dosing Schedules of TG4010 (MVA-MUC1-IL2) in Patients with Adenocarcinoma of the Prostate.* Sponsor: Transgene, Inc.

NIH/OBA Receipt Date: 9-12-01. Not Selected for RAC Public Review: 10-9-01

0109-498 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfusion/Human Telomerase Reverse Transcriptase (hTERT)/Intradermal Injections

Vieweg, Johannes, Duke University Medical Center, Durham, North Carolina; *Phase I Study of Active Immunotherapy of Metastatic, Hormone Refractory Prostate Carcinoma using Autologous Mature Dendritic Cells (DC) Transfected with RNA Encoding Human Telomerase Reverse Transcriptase (hTERT).*

NIH/OBA Receipt Date: 9-21-01. Not Selected for RAC Public Review: 10-26-01

0110-499 (Open) Gene Therapy/Phase I/Cancer/Liver (Hepatic) Metastases of Colorectal Cancer/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Sung, Max W., Mount Sinai Medical Center, New York, New York; *Clinical Trial of Adenoviral Vector Delivery of the Herpes Thymidine Kinase (HSV-tk) Gene by Intratumoral Injection Followed by Intravenous Ganciclovir with Imaging of HSV-tk Gene Expression in Patients with Hepatic Metastases from Colorectal Cancer.*

NIH/OBA Receipt Date: 10-9-01. Not Selected for RAC Public Review: 10-30-01

0110-500 (Open) Gene Therapy/Phase I/Cancer/Bladder/Pro-Drug/Ganciclovir/In Vivo/Adenovirus/Herpes Simplex Thymidine Kinase cDNA/Intratumoral Injection

Lerner, Seth P., Baylor College of Medicine, Houston, Texas; *Phase I Trial of Adenoviral Mediated Suicide Gene Therapy with HSV-tk Followed by Intravenous Administration of Ganciclovir in Patients with Locally Advanced and Refractory Superficial Bladder Cancer.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

0110-501 (Open) Gene Marking/Osteogenesis Imperfecta/In Vitro/CD34+ Cells from Donor Bone Marrow/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Infusion

Horwotz, Edwin M., St. Jude Children's Research Hospital, Memphis, Tennessee; *Treatment of Children with Severe Osteogenesis Imperfecta by Stem Cell Transplantation and Mesenchymal Cell Graft Augmentation (Pilot Study).*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0110-502 (Open) Gene Therapy/Phase II/Peripheral Artery Disease/Plasmid DNA/Fibroblast Growth Factor 1 cDNA/Intramuscular Injection

Comerota, Anthony J., Temple University School of Medicine, Philadelphia, Pennsylvania; Mendelsohn, Farrell O., Cardiology, P.C., Birmingham, Alabama; Saucedo, Jorge F., University of Arkansas for Medical Sciences, Little Rock, Arkansas; Goldman, Corey K, Watson Clinic LLP, Lakeland, Florida; Greenbaum, Adam, Henry Ford Hospital, Detroit, Michigan; Sequeira, Rafael, Jackson Memorial Hospital, Miami, Florida; Henry, Timothy, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; Miller, Julie, The Johns Hopkins University, Baltimore, Maryland; Gray, John, Durham VA Medical Center, Durham, North Carolina; Hermiller, James and Irwin, Randy, St. Vincent Hospital and Health Care Center, Indianapolis, Indiana; Moneta, Gregory, Oregon Health & Science University, Portland, Oregon; Laird, John, Washington Hospital Center, Washington, DC; Chronos, Nicolas, Atlanta Cardiology Group, Atlanta, Georgia; Kent, K. Craig, Weill Medical College of Cornell University, New York, New York; Grossman, P. Michael, The University of Michigan Health Systems, Ann Arbor, Michigan; and Eslami, Mohammad, Temple University, Philadelphia, Pennsylvania; *A Phase II, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Efficacy and Safety Study of Different Doses and Schedules of Administration of NV1FGF in Patients with Severe Peripheral Artery Occlusive Disease.* Sponsor: Aventis Pharma.

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 11-15-01

0110-503 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Nasal Epithelial Cells/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Polylysine Polyethylene Glycol Complex/Intranasal Administration

Konstan, Michael W., Case Western Reserve University, Cleveland, Ohio; and Wagener, Jeffrey, University of Colorado School of Medicine, Denver, Colorado; *Single Dose Escalation Study to Evaluate Safety of Nasal Administration of CFTR001 Gene Transfer Vector to Subjects with Cystic Fibrosis.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

0110-504 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vitro/Autologous T Lymphocytes/Retrovirus/T Cell Receptor α and β Chain cDNA/Intravenous Infusion

McDonagh, Kevin T., The University of Michigan Health System, Ann Arbor, Michigan; *A Phase I Study of Genetically Modified Autologous Peripheral Blood T-Cells Expressing a Retrovirally Encoded, MART-1 Specific αβ T-Cell Receptor, With and Without Recombinant Human Interleukin-2, in HLA-A2+.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

0110-505 (Open) Gene Therapy/Phase I/Cancer/MUC1 Expressing Carcinoma/Immunotherapy/In Vivo/Naked Plasmid DNA/MUC-1/Intramuscular Injection

Avigan, David E., Beth Israel Deaconess Medical Center, Boston, Massachusetts; *A Phase I Open-Label Study to Assess the Safety and Toxicity of Plasmid DNA MUC1 Vaccine (pMC6.5) in Metastatic Carcinoma.* Sponsor: Centocor, Inc.

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 11-12-01

0110-506 (Open) Gene Therapy/Phase I/Cancer/Melanoma/In Vitro/autologous T-Lymphocytes/Immunotherapy/Retrovirus/Interleukin-2 cDNA/Intravenous or Intra-arterial Infusion

Rosenberg, Steven A., National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Metastatic Melanoma using Lymphocytes Transduced with an Interleukin-2 (IL-2) Gene Following the Administration of a Nonmyeloablative but Lymphocyte Depleting Regimen.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 11-14-01

0110-507 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Plasmid DNA/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intradermal Injection

Wolchok, Jedd D., Memorial Sloan-Kettering Cancer Center, New York, New York; *Vaccination of AJCC Stage IIB, IIC, III and IV Melanoma Patients with a Multi-Epitope Peptide Vaccine using GM-CSF DNA as an Adjuvant: A Pilot Trial to Assess Safety and Immunity.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

0110-508 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/Antisense TAR/Antisense tat/rev/In Vitro/CD34+ Cells/Intravenous

Krishnan, Amrita, City of Hope National Medical Center, Duarte, California; *Evaluation of the Safety and Efficacy of ex vivo Modification and Re-Infusion of CD34+ Cells by an Antisense Construct against HIV-1 in a Retrovirus Vector.* Sponsor: Enzo Therapeutics, Inc.

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0111-509 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Vector Directed Cell Lysis/In Vivo/Adenovirus/Serotype 5/Repication-Comptetent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen Gene/Intratumoral Injection

Corman, John M., Virginia Mason Medical Center, Seattle Washington; *A Phase I/II Trial of Intraprostatic Injection of CG7060 Followed by Three-Dimensional Conformal Radiation Therapy (3D-CRT) in Patients with Clinically Localized Intermediate or High-Risk Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 11-9-01. Not Selected for RAC Public Review: 12-03-01

0111-510 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Prostate Specific Antigen/Intradermal Injection

Vieweg, Johannes, Duke University Medical Center, Durham, North Carolina; *Pilot Study evaluating the Migratory Patterns of Immature and In Vitro Matured Dendritic Cells Transfected with RNA Encoding PSA in Patients with Metastatic Prostate Cancer.*

NIH/OBA Receipt Date: 11-20-01. Not Selected for RAC Public Review: 12-11-01

0112-511 (Open) Gene Therapy/Phase I/Cancer Squamous Cell Carcinoma of the Head and Neck (SCCHN)/Immunotherapy/In Vitro/Allogeneic Tumor Cell/Retrovirus/Interleukin-2 cDNA/Intradermal Injection

Johnson, Jonas T., University of Pittsburgh, Pittsburgh, Pennsylvania; *Active Immunization of Patients with Carcinoma of Oral Cavity or Oropharynx with Interleukin-2-Secreting Semi-allogeneic Human Carcinoma Cell Line Transfected with DNA from Autologous Tumor (Phase I Study).*

NIH/OBA Receipt Date: 12-20-01. Not Selected for RAC Public Review: 1-14-02

0112-512 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Cachexia/In Vivo/Plasmid/Chimeric Transactivator of Progesterone Receptor-Ligand-Binding Domain Fused to the Gal4 DNA Binding Domain/Human Growth Hormone Releasing Hormone (GHRH) cDNA/Intramuscular Injection

Popat, Uday, Baylor College of Medicine, Houston, Texas; *Phase I Study of Human Growth Hormone Releasing Hormone Expressed by a Plasmid DNA Myogenic Vector in Patients with Cancer Cachexia.*

NIH/OBA Receipt Date: 12-21-01. Publicly Reviewed at the March 2002 RAC meeting

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0201-513 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer (NSCLC)/In Vivo/Tumor Suppressor Gene/Cationic Liposome Complex/DOTAP:Cholesterol/Fus 1 cDNA/Intravenous Injection

Lu, Charles, The University of Texas, MD Anderson Cancer Center, Houston, Texas; *Phase I Study of Intravenous DOTAP:Cholesterol-Fus 1 Liposome Complex (DOTAP:Chol-Fus 1) in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Previously Treated with Chemotherapy.*

NIH/OBA Receipt Date: 01-08-02. Publicly Reviewed at the March 2002 RAC meeting

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0201-514 (RAC Reviewed with Recommendations) Gene Marking/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Serotype 2/Human Placental Alkaline Phosphatase (AP or hpAP) cDNA/Nasal and Bronchial Administration

Aitken, Moira L., and Miller, A. Dusty, University of Washington, Seattle, Washington; *Transduction of the Upper and Lower Airway Epithelium in Health Subjects by an AAV2 Vector that Encodes Human Placental Alkaline Phosphatase.*

NIH/OBA Receipt Date: 01-09-02. Publicly Reviewed at the March 2002 RAC meeting

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0201-515 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Glioblastoma Multiforme/In Vivo/Herpes Simplex Virus Type 1/HSV Thymidine Kinase (TK), Connexin 43, Tumor Necrosis Factor Alpha (TNF-a), and the Viral Infected Cell Protein Zero (ICP0) Genes/Ganciclovir/Intratumoral (Stereotactic) Injections

Lunsford, L. Dade, and Glorioso, Joseph C., University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania; *Gene Therapy of Progressive Glioblastoma Multiforme using a Replication Defective HSV Multigene Vector NUREL-C2: A Phase I Clinical Trial to Determine the Maximum Tolerable Dose of Vector in Combination with Ganciclovir and Radiosurgery.*

NIH/OBA Receipt Date: 01-09-02. Publicly Reviewed at the March 2002 RAC meeting

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0201-516 (Open) Gene Therapy/Phase I-II/Monogenic Disease/X-Linked Severe Combined Immune Deficiency/In Vitro/Autologous CD34+ Cells from Peripheral Blood/Retrovirus γcDNA/Intravenous Infusion

Malech, Harry L., National Institutes of Health, Bethesda, Maryland; *Ex Vivo Retroviral Gene Transfer for Treatment of X-Linked Severe Combined Immunodeficiency (XSCID).*

NIH/OBA Receipt Date: 1-15-02. Not Selected for RAC Public Review: 2-5-02

0203-517 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Human Interferon-beta cDNA/Intratumoral Injection

Dinney, Colin P., University of Texas MD Anderson Cancer Center; *An Open Label, Dose-Escalation Study to Determine the Tolerability of Interferon-beta (BG00001) Gene Transfer in the Neoadjuvant Treatment of High-Risk Resectable Prostate Cancer.* Sponsor: Biogen, Inc.

NIH/OBA Receipt Date: 3-5-02. Not Selected for RAC Public Review: 3-25-02

0203-518 (Submission Not Complete) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Fowlpox Virus/Prostate Specific Antigen/Intradermal Injection

Phase II Randomized Study of Fowlpox PSA Vaccine with and without GM-CSF in the Treatment of Advanced Prostate Cancer. Sponsor: Eastern Cooperative Oncology Group

NIH/OBA Receipt Date: 3-11-02.

0203-519 (Open) Gene Therapy/Phase II/Cancer/Pancreas/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Plasmid/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Intradermal Injection

Laheru, Daniel, John Hopkins University School of Medicine, Baltimore, Maryland; *A Phase II Trial of CG8020 and CG2505 in Patients with Nonresectable or Metastatic Pancreatic Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 3-15-02. Not Selected for RAC Public Review: 4-4-02

0203-520 (Open) Gene Therapy/Phase I/Monogenic Disease/Fanconi Anemia/Pro-Drug/Ganciclovir/In Vitro/Allogeneic T Lymphocytes/Retrovirus/Herpes Simplex Thymidine Kinase cDNA/Graft-Versus-Host Disease/Intravenous Infusion

Orchard, Paul J., University of Minnesota Medical School, Minneapolis, Minnesota; *Transplantation of Unrelated or Mismatched Related Donor T Cells Containing the HSV-TK Suicide Gene to Facilitate Engraftment and Control Graft-Versus-Host Disease in Patients with Fanconi Anemia. A Phase I Trial.*

NIH/OBA Receipt Date: 3-21-02. Not Selected for RAC Public Review: 6-21-02

0204-521 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/End Stage Renal Disease/Stenosis Prevention/In Vivo/Adenovirus/Inducible Nitric Oxide Synthase (iNOS) cDNA/Administration at the Arteriovenous (AV) Graft for Hemodialysis Access

Tzeng, Elizabeth, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; *Inducible Nitric Oxide Synthase Gene Therapy for the Prevention of Intimal Hyperplasia in Arteriovenous Grafts used for Hemodialysis Access.*

NIH/OBA Receipt Date: 4-1-02. Publicly Reviewed at the June 2002 RAC meeting

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0204-522 (Open) Gene Therapy/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen cDNA/B7.1 (CD80) cDNA/Intramuscular or Intradermal Injection

Dahut, William, National Institutes of Health, Bethesda, Maryland; *A Pilot Trial of Concurrent Docetaxel and Pox Vector PSA Vaccine Followed by Docetaxel in Metastatic Androgen Independent Prostate Cancer.*

NIH/OBA Receipt Date: 4-9-02. Not Selected for RAC Public Review: 4-29-02

0204-523 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Ovarian/Immunotherapy/In Vivo/Measles Virus/Carcinoembryonic Antigen (CEA) cDNA/Intraperitoneal Administration

Galanis, Evanthia, Mayo Clinic, Rochester, Minnesota; *Phase I Trial of Intraperitoneal Administration of an Attenuated Strain (Edmonston Strain) of Measles Virus, Genetically Engineered to Produce CEA, in Patients with Recurrent Ovarian Cancer.*

NIH/OBA Receipt Date: 4-11-02. Publicly Reviewed at the June 2002 RAC meeting

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0204-524 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD80)/ICAM-1/LFA-3/Intramuscular or Intradermal Injection

Arlen, Philip M., National Institutes of Health, Bethesda, Maryland; *A Pilot Study of Sequential Vaccinations with Recombinant Vaccinia-CEA(6D)-TRICOM, and Recombinant Fowlpox-CEA(6D)-TRICOM (B7.1/ICAM-1/LFA-3) with Sargramostim (GM-CSF) , in Conjunction with Standard Adjuvant Chemotherapy in High Risk Breast Cancer Patients Status Post Surgery with 4+ or More Lymph Nodes and CEA Expressing Tumors*

NIH/OBA Receipt Date: 4-16-02. Not Selected for RAC Public Review: 5-6-02

0204-525 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Oncogene-Regulation/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intraperitoneal Administration

Wolf, Judith K., The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I Dose Escalation Study of Intraperitoneal tgDCC-E1A and Intravenous Carboplatin for Treatment of Recurrent, Platinum-Sensitive Ovarian Cancer.* Sponsor: Targeted Genetics Corp.

NIH/OBA Receipt Date: 4-24-02. Not Selected for RAC Public Review: 5-14-02

0204-526 (Open) Gene Therapy/Phase I/Cancer/Colon Carcinoma (Hepatic Metastasis)/Herpes Simplex Virus Type-1/Tumor Lysis/Intrahepatic Artery Administration

Fong, Yuman, Memorial Sloan-Kettering Cancer Center, New York, New York; *A Phase I, Open-Label, Dose-Escalating Study of Safety, Tolerability, and Anti-Tumor Activity of a Single Intrahepatic Arterial Injection of a Genetically Engineered Herpes Simplex Virus, NV1020, in Herpes Simplex Seronegative Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 4-23-02. Not Selected for RAC Public Review: 5-13-02

0204-527 (Open) Gene Therapy/Phase I/Cancer/Colon Carcinoma (Hepatic Metastasis)/Herpes Simplex Virus Type-1/Tumor Lysis/Intrahepatic Artery Administration

Fong, Yuman, Memorial Sloan-Kettering Cancer Center, New York, New York; *Long-Term Follow-Up of the Safety and Survival of HSV Simplex Seronegative Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver Who Enrolled in a Phase I Dose-Escalating Study Evaluating Genetically Engineered Herpes Simplex Virus, NV1020.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 4-23-02. Not Selected for RAC Public Review: 5-13-02

0204-528 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Other Disorders/Erectile Dysfunction/In Vivo/Plasmid/Human Maxi-K Channel hSlo cDNA/Intracavernous Injection

Melman, Arnold, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York; *Pilot Study of the Human hslo/maxi-K Gene to Treat Erectile Dysfunction.*

NIH/OBA Receipt Date: 4-23-02. Publicly Reviewed at the June 2002 RAC meeting

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0204-529 (RAC Reviewed with Recommendations) Gene Therapy/Other Disorders/Intractable Pain/In Vivo/Herpes Simplex Virus Type 1/Proenkephalin/Subcutaneous Inoculation

Fink, David, and Glorioso, Joseph, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; *Gene Transfer for Intractable Pain: A Phase I Clinical Trial to Determine the Maximum Tolerable Dose of a Replication Defective HSV Vector Expressing Human Proenkephalin.*

NIH/OBA Receipt Date: 4-24-02. Publicly Reviewed at the June 2002 RAC meeting

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0204-530 (Open) Gene Therapy/Phase II/Cancer/Pancreatic Cancer/Immunotherapy/In Vivo/Adenovirus/Type 5/Tumor Necrosis Factor cDNA/Intratumoral Injection

Senzer, Neil Nathan, U.S. Oncology, Inc., Dallas Texas; Richards, Donald, Tyler Care Center, Tyler, Texas; Hecht, J. Randolph, UCLA Medical Center, Los Angeles , California; Hanna, Nader, University of Kentucky, Lexington, Kentucky; Chung, Theodore D.K., Virginia Commonwealth University, Richmond, Virginia; Vogel, Stephen, The University of Florida, Gainesville, Florida; Reid, Tony, Palo Alto VA Health Care Systems, Palo Alto, California; Chang, Kenneth J., University of California, Irvine, Orange, California; Javle, Milind, Roswell Park Cancer Institute, Buffalo, New York; Erickson, Richard, Scott & White Memorial Hospital and Clinic, Temple, Texas; and Rosemurgy, Alexander, University of South Florida, Tampa, Florida; *A Randomized, Phase II, Study of TNFerade™ Biologic with 5-FU and Radiation Therapy for First-Line Treatment of Unresectable Locally Advanced Pancreatic Cancer.* Sponsor: GenVec, Inc.

NIH/OBA Receipt Date: 4-24-02. Not Selected for RAC Public Review: 5-14-02

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0204-531 (Open) Gene Therapy/Cancer/Mesothelioma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Interferon-beta/Intrapleural Administration

Sterman, Daniel, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *A Phase I Trial of Intrapleural Gene Therapy of Malignant Pleural Disease Using E1-Deleted Adenoviruses Containing the Human Interferon Beta Gene.*

NIH/OBA Receipt Date: 4-24-02. Not Selected for RAC Public Review: 5-14-02

0204-532 (Closed) Gene Therapy/Other Disorders/Peripheral Arterial Occlusive Disease (PAOD)/In Vivo/Adenovirus/Serotype 5/Fibroblast Growth Factor (FGF) cDNA/Intramuscular Injection

Haser, Paul B., St. Michael's Medical Center, Newark, New Jersey; *Double-Blind, Randomized, Placebo-Controlled Study of Ascending Doses on Tolerability of Ad5.1 Mediated Human FGF-4 Gene Transfer Given Intramuscularly on One Day in Patients with Peripheral Arterial Occlusive Disease (PAOD) Fontaine Stage III or Fontaine Stage IV.* Sponsor: Berlex Laboratories.

NIH/OBA Receipt Date: 4-24-02. Not Selected for RAC Public Review: 7-10-02
Closed: 12-16-02

0204-533 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Prostate/Radiotherapy/In Vivo/Adenovirus/Serotype 5/Human Sodium-Iodide Symporter (NIS) cDNA/Intratumoral Injection

Morris, John C., Mayo Clinic, Rochester, Minnesota; *Phase I Trial of In Situ Gene Therapy for Locally Recurrent Prostate Cancer Following Radiation Therapy Failure Using Sodium/Iodide Symporter and Radioiodine.*

NIH/OBA Receipt Date: 4-25-02. Publicly Reviewed at the June 2002 RAC meeting

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0204-534 (RAC Reviewed with Recommendations) Non-therapeutic (Healthy Volunteers)/Phase I/In Vivo/Adenovirus/Serotype 4/Human Immunodeficiency Virus-1 env Plus rev or gag/Protease Plus rev Inserted Genes/Oral or Intranasal Administration

Connors, Mark, National Institutes of Health, Bethesda, Maryland; *Phase I Study of AD4-ΔE3-HIV$_{env}$ and AD4-ΔE3-HIV$_{gag/pro}$ Recombinant Vaccines in HIV-negative Volunteers.*

NIH/OBA Receipt Date: 4-24-02. Publicly Reviewed at the June 2002 RAC meeting

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0205-535 (Open) Gene Therapy/Phase I/Cancer/Acute Lymphoblastic Leukemia (ALL)/Immunotherapy/In Vitro/Plasmid DNA/Chimeric T Cell Receptor (CD19R) cDNA/Fusion Gene Encoding Hygromycin Phosphotransferase and Herpes Simplex Thymidine Kinase (HyTK)/Intravenous Infusion

Cooper, Laurence J. N., City of Hope Medical Center, Duarte, California; *Phase I Study to Evaluate the Safety of Cellular Immunotherapy for High-Risk CD19+ Acute Lymphoblastic Leukemia after Autologous Hematopoietic Stem Cell Transplantation using Genetically Modified CD19-redirected Autologous Cytolytic T Cell Clones.*

NIH/OBA Receipt Date: 5-6-02. Not Selected for RAC Public Review: 5-28-02

0205-536 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen (PSA)/B7.1 (CD80)/ICAM-1/LFA-3/Subcutaneous Injection

Kaufman, Howard L., Columbia University, New York, New York; Plante, Mark, The University of Vermont, Burlington, Vermont; and DiPaola, Robert, Robert Wood Johnson Medical School, New Brunswick, New Jersey; *Phase I Open Label Study to Evaluate the Safety of PROSTVAC-VF-TRICOM in the Treatment of Subjects with Adenocarcinoma of the Prostate.* Sponsor: Therion Biologics Corporation.

NIH/OBA Receipt Date: 5-16-02. Not Selected for RAC Public Review: 6-26-02

0205-537 (Open) Gene Therapy/Phase I-II/Cancer/Breast/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD80)/ICAM-1/LFA-3/Intramuscular Or Intradermal Injection

Kasten-Sportes, Claude, National Institutes of Health, Bethesda, Maryland; *A Phase I-II Study of Tumor Antigen (CEA) Immunization with Autologous Peripheral Progenitor Cell Transplantation in Patients Previously Untreated for Metastatic Breast Cancer.*

NIH/OBA Receipt Date: 5-24-02. Not Selected for RAC Public Review: 6-14-02

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0205-538 (Open) Gene Therapy/Phase I-II/Cancer/Small Cell Lung Cancer/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/p53 cDNA/Intradermal Injection

Antonia, Scott J., University of South Florida, Tampa, Florida; *A Phase I-II Trial Using Dendritic Cells Transduced with an Adenoviral Vector Containing the p53 Gene to Immunize Patients with Extensive Stage Small Cell Lung Cancer after Standard Chemotherapy.*

NIH/OBA Receipt Date: 5-24-02. Not Selected for RAC Public Review: 6-14-02

0206-539 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Other Disorders/Superficial Corneal Opacity/Corneal Scarring/InVivo/Retrovirus/dnG1 Cyclin/Eye Administration (Ophthalmic Instillation)

Song, Jonathan C., Keck School of Medicine, University of Southern California, Los Angeles, California; *Phase I/II Evaluation of Safety and Efficacy of a Matrix-Targeted Retroviral Vector Bearing a Dominant Negative Cyclin G1 Construct (Mx-dnG1) as Adjunctive Intervention for Superficial Corneal Opacity/Corneal Scarring.*

NIH/OBA Receipt Date: 6-5-02. Publicly Reviewed at the September 2002 RAC meeting

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0206-540 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Oncogene-Regulation/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intraperitoneal Administration

Wolf, Judith K., The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I Dose Escalation Study of Intraperitoneal tgDCC-E1A and Intravenous Paclitaxel in Women with Platinum-Resistant Ovarian Cancer.* Sponsor: Targeted Genetics Corp.

NIH/OBA Receipt Date: 6-6-02. Not Selected for RAC Public Review: 6-26-02

0206-541 (Open) Gene Therapy/Phase I-II/Cancer/Breast/Immunotherapy/In Vivo/Naked Plasmid/Gene Encoding NY-ESO-1 Epitope/Intralymphnodal Injection

Waisman, James R., University of Southern California, Los Angeles, California; *A Phase I/II Study of Intranodal Delivery of Synchrovax BPL Vaccine, an Epitope Synchronization Plasmid DNA Vaccine, in Sage IV Breast Carcinoma Patients.* Sponsor: CTL ImmunoTherapies Corporation.

NIH/OBA Receipt Date: 6-13-02. Not Selected for RAC Public Review: 7-18-02

0207-542 (Open) Gene Therapy/Phase I-II/Cancer/Pancreas/Pro-Drug/Valacyclovir/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Intratumoral Injection

Fernandez-del Castillo, Carlo, Massachusetts General Hospital, Boston, Massachusetts; and Aguilar-Cordova, Estuardo, Harvard Gene Therapy Initiative, Boston, Massachusetts; *AdV-tk Gene Therapy in Combination with Chemoradiation for Locally Advanced Pancreatic Cancer.*

NIH/OBA Receipt Date: 7-17-02. Not Selected for RAC Public Review: 8-6-02

0207-543 (Open) Gene Therapy/Phase I/Cancer/Follicular Lymphoma/Immunotherapy/In Vitro/Plasmid DNA/Chimeric T Cell Receptor (CD19R) cDNA/Fusion Gene Encoding Hygromycin Phosphotransferase and Herpes Simplex Virus Thymidine Kinase

Cooper, Laurence J. N., City of Hope National Medical Center, Duarte, California; *Phase I Study to Evaluate the Safety of Cellular Immunotherapy for CD 19+ Follicular Lymphoma Using Autologous T Cell Cytolytic Clones Genetically Modified to be CD19-Specific and Express HyTK.*

NIH/OBA Receipt Date: 7-18-02. Not Selected for RAC Public Review: 8-7-02

0207-544 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Melanoma/Pro-Drug/Valacyclovir/In Vivo/DNA-Liposome Complexes/Herpes Simplex Thymidine Kinase cDNA/Intravenous Injection

Thompson, John A., Seattle Cancer Care Alliance and The University of Washington, Seattle, Washington; *A Phase I Study to Evaluate the Safety and Pharmacokinetics of Pro-1, a Liposome-Encapsulated Thymidine Kinase Gene Formulation, in Patients with Stage IV Metastatic Melanoma.* Sponsor: Protiva Biotherapeutics, Inc.

NIH/OBA Receipt Date: 7-24-02. Publicly Reviewed at the September 2002 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0207-545 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Peripheral Blood Lymphocytes/Plasmid DNA/Immunoglobulin Heavy (H) Chain Gene/Telomerase Reverse Transcriptase (hTERT) Gene/Intravenous Infusion

Zanetti, Maurizio, University of California, San Diego, San Diego, California; *A Phase I/II, Escalating Dose, Open Label Evaluation of Safety, Feasibility and Tolerability of Transgenic Lymphocyte Immunization Vaccine (TLI) in Subjects with Histologically Proven Prostate Adenocarcinoma.* Sponsor: Cosmo Bioscience, Inc.
NIH/OBA Receipt Date: 7-24-02. Publicly Reviewed at the September 2002 RAC meeting

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0207-546 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Peripheral Artery Disease/Plasmid DNA/Hepatocyte Growth Factor cDNA/Intramuscular Injection

Powell, Richard J., Dartmouth Medical School, Lebanon, New Hampshire; *A Phase I/II Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety and Efficacy of AMG0001 to Improve Perfusion in Critical Leg Ischemia.* Sponsor: AnGes, Inc.

NIH/OBA Receipt Date: 7-24-02. Publicly Reviewed at the September 2002 RAC meeting

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0207-547 (Withdrawn from RAC Review) Gene Therapy/Phase I-II/Peripheral Artery Disease/Plasmid DNA/Hepatocyte Growth Factor cDNA/Intramuscular Injection

Powell, Richard J., Dartmouth Medical School, Lebanon, New Hampshire; *A Phase I/II Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety and Efficacy of AMG0001 to Improve Perfusion and Healing After Major Amputation Due to Critical Leg Ischemia.* Sponsor: AnGes, Inc.

NIH/OBA Receipt Date: 7-24-02. Withdrawn from RAC review: 9-6-02.

0207-548 (Open) Gene Therapy/Phase I/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Total Tumor RNA/Intravenous Infusion

Vieweg, Johannes and Chao, Nelson, Duke University Medical Center, Durham, North Carolina; *Active Immunotherapy with Mature, Tumor RNA-Transfected, Autologous Dendritic Cells with or without the IL2-Diphtheria Toxin Conjugate Denileukin Difitox (Ontak®) in Patients with Metastatic Renal Cell Carcinoma.*

NIH/OBA Receipt Date: 7-29-02. Not Selected for RAC Public Review: 8-16-02

0208-549 (Open) Gene Therapy/Phase II/Cancer/Esophagus/Immunotherapy/In Vivo/Adenovirus/Type 5/Tumor Necrosis Factor cDNA/Intratumoral Injection

Senzer, Neil, US Oncology, Dallas, Texas; *A Phase II, Multi-Center, Single Arm Evaluation of Preoperative Chemoradiation Plus TNFerade™ Biologic ($Ad_{GV}EGR.TNF.11D$) Prior to Esophagectomy for Locally Advanced Esophageal Cancer.* Sponsor: GenVec.

NIH/OBA Receipt Date: 8-1-02. Not Selected for RAC Public Review: 8-21-02

0208-550 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Breast/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Retrovirus/α-(1,3) galactosyltransferase Gene/Subcutaneous Injection

Morton, Roscoe F., Iowa Methodist Medical Center, Des Moines, Iowa; *A Phase I/II Study of an Antitumor Vaccination Using α(1,3) galactosyltransferase Expressing Allogeneic Tumor Cells in Patients with Relapsed or Refractory Breast Cancer.* Sponsor: NewLink Genetics Corporation

NIH/OBA Receipt Date: 8-26-02. Publicly Reviewed at the December 2002 RAC meeting

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0210-551 (Open) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/Vaccinia Virus/Tyrosinase cDNA/Intramuscular Injection

Topalian, Suzanne, National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Metastatic Melanoma using Recombinant Vaccinia and Fowlpox Viruses Encoding the Tyrosinase Antigen in Combination with Interleukin-2.*

NIH/OBA Receipt Date: 10-3-02. Not Selected for RAC Public Review: 10-24-02

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0210-552 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Retrovirus/α(1, 3)galactosyltransferase Gene/Subcutaneous Injection

Morris, John C., National Institutes of Health, Bethesda, Maryland; *A Phase I/II Study of an Antitumor Vaccination using α(1, 3)galactosyltransferase Expressing Allogeneic Tumor Cells in Patients with Refractory or Recurrent Non-Small Cell Lung Cancer.* Sponsor: NewLink Genetics Corporation

NIH/OBA Receipt Date: 10-9-02. Publicly Reviewed at the December 2002 RAC meeting

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0210-553 (Open) Gene Therapy/Phase I/Cancer/Chronic Lymphocytic B-Leukemia/Immunotherapy/In Vitro/Plasmid DNA/Interleukin-2/CD40 Ligand/Subcutaneous Injections

Brenner, Malcolm, Baylor College of Medicine, Houston, Texas; *Treatment of Chronic Lymphocytic B-Leukemia (B-CLL) with Human IL-2 and Human CD40 Ligand Plasmid Gene Modified Autologous Tumor Cells.*

NIH/OBA Receipt Date: 10-9-02. Not Selected for RAC Public Review: 10-30-02

0210-554 (Open) Non-therapeutic (Healthy Volunteers)/Phase I/Infectious Diseases/Human Immunodeficiency Virus/In Vivo/Plasmid/HIV-1 Gag-Pol-Nef-Env cDNA/Interleukine-2 (IL-2)/Ig Fusion Protein/Bioinjector 2000® Injections

Dolin, Raphael, Harvard Medical School, Boston Massachusetts; Blattner, William, University of Maryland, Baltimore, Maryland; and Hammer, Scott Columbia University/New York Blood Center, New York, New York; *A Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of the HIV-1 DNA Vaccine VRC-HIVDNA009-00-VP (Gag-Pol-Nef-Multiclade Env) with the Plasmid Cytokine Adjuvant VRC-ADJDNA004-IL2-VP (IL-2/Ig).*

NIH/OBA Receipt Date: 10-9-02. Not Selected for RAC Public Review: 10-30-02

0210-555 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Plasmid/Prostate Specific Antigen (PSA)/Intramuscular Injection

Malkowicz, S. Bruce, University of Pennsylvania Health System, Philadelphia, Pennsylvania; *A Phase I Study of a Polynucleotide Anti-Tumor Immunization to Human Prostate Specific Antigen (PSA) in Patients with Hormone-Refractory Prostate Cancer (HRPC).* Sponsor: Centocor Inc.

NIH/OBA Receipt Date: 10-9-02. Not Selected for RAC Public Review: 10-30-02

0210-556 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vivo/Plasmid DNA/Adenovirus/Serotype 5/L523S cDNA/Intramuscular Injection

Nemunaitis, John J., US Oncology, Dallas, Texas; *Phase I Open-Label, Dose Escalation Trial Evaluating the Safety and Immunogenicity of Sequential Administration of Recombinant DNA and Adenovirus Expressing L523S Protein in Patients with Early Stage Non-Small Cell Lung Cancer.* Sponsor: Corixa Corporation

NIH/OBA Receipt Date: 10-9-02. Publicly Reviewed at the December 2002 RAC meeting

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0210-557 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Coronary Artery Disease/Plasmid DNA/Hepatocyte Growth Factor cDNA/Intramyocardial Injection

Simons, Michael, Dartmouth Medical School, Lebanon, New Hampshire; and Annex, Brian H., Duke University School of Medicine, Durham VA Medical Center, Durham, North Carolina; *A Double-Blind, Placebo-Controlled, Dose Escalation Pilot Study to Assess the Safety and Effects of AMG0001 in Patients with Ischemic Heart Disease (IHD) not Amenable to Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI).* Sponsor: AnGes, Inc.

NIH/OBA Receipt Date: 10-9-02. Publicly Reviewed at the December 2002 RAC meeting

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0212-558 (Open) Gene Therapy/Phase I-II/Cancer/Breast/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/Serotype 5/p53 cDNA/Subcutaneous Injection

Reed, Elizabeth C., University of Nebraska Medical Center, Omaha, Nebraska; *Adenovirus p53 Infected DC Vaccine for Breast Cancer.*

NIH/OBA Receipt Date: 12-9-02. Not Selected for RAC Public Review: 1-13-03

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0212-559 (Open) Gene Therapy/Phase I/Cancer/Pancreas/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD80)/ICAM-1/LFA-3/MUC-1/Subcutaneous Injection

Kaufman, Howard L., Columbia University, New York, New York; *An Open Label Phase I Study to Evaluate the Safety and Tolerability of rV-CEA(6D)/TRICOM™ Admixed with rV-MUC-1 followed by rF-CE(6D)/TRICOM™ in Combination with GM-CSF in Subjects with Unresectable Adenocarcinoma of the Pancreas.* Sponsor: Therion Biologics Corporation.

NIH/OBA Receipt Date: 12-10-02. Not Selected for RAC Public Review: 1-06-03

0212-560 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen (PSA)/B7.1 (CD80)/ICAM-1/LFA-/GM-CSF/Intramuscular Or Intradermal Injection

Arlen, Philip M., National Institutes of Health, Bethesda, Maryland; *A Phase I/II Pilot Study of Sequential Vaccinations with rFOWLPOX-PSA (L155)-TRICOM (PROSTAVAC-F/TRICOM) Alone, or in Combination with rVACCINIA-PSA (L155)-TRICOM (PROSTAVAC-V/TRICOM) and the Role of GM-CSF, in Patients with Prostate Cancer.* Sponsor: Therion Biologics Corporation.

NIH/OBA Receipt Date: 12-10-02. Not Selected for RAC Public Review: 1-06-03

0212-561 (Open) Gene Therapy/Phase I/Cancer/Pancreas/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Plasmid/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Intradermal Injection

Shuman, Marc, University of California, San Francisco Cancer Center, San Francisco, California; *Pancreatic GVAX® for Resected Adenocarcinoma of the Pancreas.*

NIH/OBA Receipt Date: 09-04-02. Not Selected for RAC Public Review: 1-03-03

0212-562 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/In Vitro/Allogeneic K562 Cell/Combination With Untransduced Tumor Cells/Plasmid DNA/Electroporation/DMRIE-Cholesterol/Granulocyte-macrophage Colony Stimulating Factor cDNA/CD40 Ligand cDNA/Intradermal Injection

Dessureault, Sophie, University of South Florida, Tampa, Florida; *A Phase I Trial Using a Universal GM-CSF-Producing and CD40L-Expressing Bystander Cell Line (GM.CD40L) in the Formulation of Autologous Tumor Cell-Based Vaccines for Cancer Patients with Stage IV Disease.*

NIH/OBA Receipt Date: 12-18-02. Not Selected for RAC Public Review: 1-10-03

0212-563 (Under Review) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Autologous T Lymphocytes/Retrovirus/GD-2 Specific scFvFc-Zeta T Cell Receptor/Intravenous Injections

Russell, Heidi, and Brenner, Malcolm, Baylor College of Medicine, Houston, Texas; *Administration of Peripheral Blood T-Cells and EBV Specific CTLs Transduced to Express GD-2 Specific Chimeric T Cell Receptors to Patients with Neuroblastoma.*

NIH/OBA Receipt Date: 12-24-02.

0301-564 (Under Review) Gene Therapy/Phase I/Cancer Adenocarcinoma Expressing Carcinoembryonic Antigen (CEA)/Immunotherapy/In Vitro/Autologous T Lymphocytes/Retrovirus/Anti-CEA-sFv-Zeta T Cell Receptor-CD28/Intravenous Infusion

Junghans, Richard, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; *Phase Ia/Ib Trial of 2nd Generation Designer T Cells in Adenocarinoma.*

NIH/OBA Receipt Date: 1-06-03.

0301-565 (Closed) Gene Therapy/Phase I/Anaplastic Thyroid Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5 p53 cDNA/Intratumoral Injections

Reid, William K., Vanderbilt-Ingram Oncology, Vanderbilt University Medical Center, Franklin, Tennessee; *Study to Evaluate the Overall Response and Safety of Biweekly Intratumoral Administration of RPR/INGN 201 in Anaplastic Thyroid Cancer.*

NIH/OBA Receipt Date: 1-06-03. Not Selected for RAC Public Review

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0301-566 (Under Review) Gene Therapy/Phase I/Cancer/Hematologic Malignancy Following Allogeneic Bone Marrow Transplantation/Pro-drug/Elimination of Graft Versus Host Disease/In Vitro/Allogeneic T Cells/Retrovirus/CD34-Herpes Simplex Virus Thymidine Kinase cDNA/Gangiclovir/Intravenous

DiPersio, John, Washington University School of Medicine, St. Louis, Missouri; *Infusion of Genetically Modified T Cells: Tracking and Toxicity.*

NIH/OBA Receipt Date: 1-07-03.

0301-567 (Open) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Percutaneous Cardiac Catheterization/Intra-myocardial Injection

Losordo, Douglas W., St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston Massachusetts; *A Multicenter, Randomized, Double-Blind, Dose Ranging Placebo Controlled Study Evaluating Defined Doses of Percutaneously Delivered pVGl.1 (VEGF2) (Placebo, 2, 200, or 2000 µg) in "No Option" Patients with Class III or IV Angina with an Option for Patients to Receive Active Treatment at Month 6 if they Experience a Treatment Failure.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/OBA Receipt Date: 1-08-03. Not Selected for RAC Public Review: 1-29-03

0301-568 (Open) Gene Therapy/Phase II/Peripheral Artery Disease/In Vivo/DNA-Liposome Complexes/Poloxamer 188/Del-1 cDNA/Intramuscular Injection

Rajagopalan, Sanjay, University of Michigan, Ann Arbor, Michigan; *A Phase II Multi-Center, Double-Blind, Placebo-Controlled, Trial of VLTS-589 in Subjects with Intermittent Claudication Secondary to Peripheral Arterial Disease.* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 1-08-03. Not Selected for RAC Public Review: 1-29-03

0301-569 (Open) Gene Therapy/Phase II/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) cDNA/Aerosol Administration

Moss, Richard, Stanford University School of Medicine, Palo Alto, California; *A Multicenter, Double-Blind, Placebo-Controlled, Phase II Study of Aerosolized tgAAVCF for the Treatment of Cystic Fibrosis.* Sponsor: Targeted Genetics Corporation.

NIH/OBA Receipt Date: 1-08-03. Not Selected for RAC Public Review: 1-29-03

0301-570 (Under Review) Non-therapeutic (Healthy Volunteers/Cholera Vaccine/In Vivo/*Vibrio cholerae*/Oral Administration

Tacket, Carol O., Center for Vaccine Development, University of Maryland, Baltimore, Maryland; *Use of in vivo Expression Technology to Identify Virulence Factors and Protective Antigens of Vibrio cholerae 01.*

NIH/OBA Receipt Date: 1-08-03.

(Scroll down for Summary Table)

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

HUMAN GENE TRANSFER PROTOCOLS
(please see explanation of review levels below)

	Review Level 1	Review Level 2	Review Level 3	Review Level 4	Review Level 5	Review Level 6	Review Level 7	TOTAL
MARKING	23	2	5	0	0	10	1	41
THERAPY	83	5	92	5	11	255	61	512
NON-THERAPEUTIC	1	0	0	0	1	1	2	5
INFECTIOUS DISEASES	8	1	11	1	1	14	2	38
1. Human Immunodeficiency Virus	8	1	11	1	1	13	2	37
2. Epstein Barr Virus/Cytomegalovirus Disease	0	0	0	0	0	1	0	1
MONOGENIC DISEASES	20	1	9	0	1	15	11	57
1. Alpha-1-Antitrypsin Deficiency	1	0	0	0	0	1	0	2
2. Chronic Granulomatous Disease	1	0	1	0	0	1	0	3
3. Cystic Fibrosis	10	1	5	0	0	6	1	23
4. Familial Hypercholesterolemia	1	0	0	0	0	0	0	1
5. Fanconi Anemia	1	0	0	0	0	3	0	4
6. Gaucher Disease	3	0	0	0	0	0	0	3
7. Hunter Syndrome	1	0	0	0	0	0	0	1
8. Ornithine Transcarbamylase Deficiency	0	0	1	0	0	0	0	1
9. Purine Nucleoside Phosphorylase Deficiency	1	0	0	0	0	0	0	1
10. SCID	1	0	1	0	0	3	1	6
11. Leukocyte Adherence Deficiency	0	0	1	0	0	0	0	1
12. Canavan Disease	0	0	0	0	0	1	2	3
13. Hemophilia	0	0	0	0	0	0	5	5
14. Muscular Dystrophy	0	0	0	0	0	0	1	1
15. Amyotrophic Lateral Sclerosis	0	0	0	0	1	0	0	1
16. Junctional Epidermolysis Bullosa	0	0	0	0	0	0	1	1
OTHER DISEASES / DISORDERS	2	0	2	2	2	31	20	59
1. Peripheral Artery Disease	1	0	0	1	1	16	1	20
2. Rheumatoid Arthritis	1	0	0	0	0	0	1	2
3. Arterial Restenosis	0	0	1	0	0	1	1	3
4. Cubital Tunnel Syndrome	0	0	1	0	0	0	0	1
5. Coronary Artery Disease	0	0	0	1	0	13	5	19
6. Alzheimer's Disease	0	0	0	0	0	0	1	1
7. Ulcer	0	0	0	0	0	1	2	3
8. Bone Fracture	0	0	0	0	1	0	0	1
9. Renal Disease	0	0	0	0	0	0	3	3
10. Peripheral Neuropathy	0	0	0	0	0	0	1	1
11. Parkinson's Disease	0	0	0	0	0	0	1	1
12. Eye Disorders	0	0	0	0	0	0	2	2
13. Erectile Dysfunction	0	0	0	0	0	0	1	1
14. Intractable Pain	0	0	0	0	0	0	1	1
CANCER *(BY THERAPEUTIC APPROACH)*	53	3	70	2	7	195	28	358
1. Antisense	4	0	0	0	0	2	0	6
2. Chemoprotection	4	0	4	0	0	4	0	12
3. Immunotherapy/In Vitro Transduction	22	2	19	0	4	57	3	107
4. Immunotherapy/In Vivo Transduction	7	0	28	1	2	80	6	124
5. Pro-drug/HSV-TK and Ganciclovir	12	1	10	0	1	12	6	42
6. Tumor Suppressor Gene	3	0	6	0	0	24	3	36
7. Single Chain Antibody	0	0	2	0	0	0	0	2
8. Oncogene Down-Regulation	1	0	1	1	0	6	0	9
9. Vector-Directed Cell Lysis	0	0	0	0	0	10	6	16
10. Dominant Negative Mutation	0	0	0	0	0	0	2	2
11. Gene Up-Regulation	0	0	0	0	0	0	1	1
12. Radiotherapy	0	0	0	0	0	0	1	1
TOTAL GENE TRANSFER PROTOCOLS *(THERAPY, MARKING and NON-THERAPEUTIC)*	107	7	97	5	12	266	64	*558

Note:** **The total number of protocols on the above list does not equal the total number that has been or will be reviewed by the RAC. Protocol 9903-295 has been withdrawn; Protocol 9907-331 was replaced by protocol 0004-393; Protocols 9910-347 and 9910-348 have been withdrawn; Protocol 9910-349 was replaced by protocol 0010-427; Protocol 0001-374 was replaced by protocol 0007-407; Protocol 0001-375 was replaced by protocol 0010-425; Protocol 0001-377 has been withdrawn; Protocols 0001-383 and 0001-384 have been withdrawn; Protocol 0107-492 was replaced by protocol 0110-499; Protocol 0207-547 has been withdrawn.

Review Level 1 = Full RAC review + NIH Director approval + FDA Investigational New Drug (IND) approval. This review process is no longer in effect.

Review Level 2 = Accelerated RAC Review + NIH Office of Recombinant DNA Activities (ORDA) Approval + FDA IND Approval. This review process is no longer in effect.

Review Level 3 = Sole FDA Review Recommended by NIH/ORDA. Simultaneous submission to NIH(ORDA) required for the purpose of data monitoring and adverse event reporting. This review process is no longer in effect.

Review Level 4 = Sole FDA Review [submission to NIH(OBA) not required]. This is only for non-NIH funded (either direct or collaborative) institutions who elect to submit to NIH(OBA) under voluntary compliance.

Review Level 5 = Received by NIH(OBA). Review level pending.

Review Level 6 = Not Selected for RAC Public Review. Submission to NIH(OBA) required for the purpose of data monitoring and adverse event reporting. This review process is currently in effect.

Review Level 7 = Full RAC discussion + FDA approval. This review process is currently in effect.

Cancer Gene Therapy (2003) 10, 224–238

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Assessment of p53 gene transfer and biological activities in a clinical study of adenovirus-p53 gene therapy for recurrent ovarian cancer

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A cohort study was designed to evaluate the efficiency of gene transfer and whether biological activity from the expressed therapeutic gene resulted after administration of a recombinant adenovirus containing the human wild-type p53 ($p53^{wt}$) gene (rAd-p53 SCH 58500). The cohort study was conducted in five trial subjects with recurrent ovarian cancer. Each trial subject received multiple cycles of rAd-p53 SCH 58500, each cycle comprised of doses of 7.5×10^{13} particles on each of five consecutive days. Subjects were treated with rAd-p53 SCH 58500 alone during Cycle 1 and in combination with gemcitabine during the subsequent cycles. Both tumor biopsies and peritoneal aspirates were collected and evaluated for gene transfer and evidence of the biological activities of the expressed $p53^{wt}$ gene. Using quantitative PCR and RT-PCR, and *in situ* PCR, gene transfer and expression were documented in tumor biopsies (four of five patients) collected from Cycle 1. Furthermore, upregulation of p21/WAF1, bax and mdm-2, and downregulation of survivin were observed in these same tumor biopsy samples, suggesting that intraperitoneal administration of rAd-p53 SCH 58500 leads to detectable p53 biological activity in target tumor tissue. In addition, gene transfer and its expression were observed in cells obtained from peritoneal aspirates. These fluids were mainly comprised of polymorphonuclear neutrophils, indicating that successful gene transfer can be achieved by multiple cycle intraperitoneal administration of recombinant adenovirus.

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Keywords: rAd-p53; ovarian cancer; gene therapy; QPCR; SCH 58500

rAd-p53 SCH 58500 is a replication-deficient adenovirus encoding the p53 tumor-suppressor gene and has been studied in human subjects with melanoma, breast cancer,[1] small-cell lung cancers,[2,3] bladder cancers,[4] liver,[5] and ovarian cancers.[6,7] These studies established the safety and feasibility of regional injections of rAd-p53 SCH 58500 for cancer. Evidence of p53 gene transfer was also shown for most of the human subjects who received high doses of rAd-p53 SCH 58500. Extensive safety data and gene transfer information have also been reported by other investigators using recombinant adenoviral (rAd) gene transfer in various clinical trials.[8–12] While many of these initial protocols have demonstrated the feasibility of using recombinant adenovirus to deliver genes to tumors in humans, further investigation is required to understand the potential for effective gene therapy with this delivery system.

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In this study we investigated: (1) whether the gene was delivered to the tumors of human subjects using a recombinant adenovirus vector, (2) whether the delivered gene demonstrated the anticipated transcriptional activity of human $p53^{wt}$, and (3) whether repeat administration of a recombinant adenovirus will result in significant gene transfer. To this end, we designed a clinical protocol to evaluate the efficiency of gene transfer after multiple cycles of rAd-p53 SCH 58500 and measured the expression of genes known to be transcribed by p53.

It has been reported in clinical studies that a single intraperitoneal administration of a recombinant adenovirus vector carrying the gene encoding thymidine kinase[13] or anti-erbB-2 single-chain antibody[10] can result in detectable biological activity of the therapeutic gene. However, in these studies only low levels of gene transfer and expression were observed in tumors. The authors of these studies have also suggested that changing the dose regimen to include multiple administrations of the rAd might be a means to enhance the therapeutic benefit. In fact, favorable clinical responses have been reported in

several clinical studies where administration of a rAd vector expressing $p53^{wt}$ gene over multiple cycles was employed to achieve a greater degree of gene transfer.[6–8] Animal studies have shown that high titers of antiadenovirus antibodies detected in animals previously treated with recombinant adenoviruses caused transduction efficiency to be diminished or completely abrogated during subsequent dosing.[14,15] It has therefore been the subject of debate as to whether multiple dosing strategies for recombinant adenoviruses are likely to be effective in increasing or maintaining levels of transgene expression in humans. Therefore, we believed that a careful evaluation of gene transfer and expression in human subjects scheduled to receive multiple cycles of a rAd would provide helpful information in evaluating a multiple dosing strategy.

To address this issue, we enrolled five additional subjects into a phase I/II trial with a multiple cycle administration schema for rAd-p53 SCH 58500 administration to human subjects with recurrent ovarian cancer.[6,7] In this subcohort of individuals with recurrent ovarian cancer, we focused on the levels of p53 transgene expression and the assessment of p53 transcriptional activity during multiple cycle administration of rAd-p53 SCH 58500.

It has been shown in preclinical studies that the introduction of the $p53^{wt}$ gene into tumor cells lacking functional p53 results in antitumor activity through transcriptional regulation of genes involved in apoptosis and/or cell cycle arrest.[16,17] In addition to gene delivery, it is important to know whether the gene delivered to the trial subjects has biological activity. The $p53^{wt}$ gene can activate genes such as p21/WAF1 and bax[18–21] to induce G1 arrest and allow cells to repair DNA prior to proceeding to proliferation,[22] or to accelerate cell apoptosis.[23] Recently, Mirza et al.[32] suggested that $p53^{wt}$ represses survivin expression, a member of the inhibitor of apoptosis (IAP) gene family. A feedback loop regulation between the mdm-2 and p53 genes has also been reported in various studies.[24,25] Upregulation of mdm-2 by overexpression of $p53^{wt}$ can result in the repression of p53 transcriptional functions. Therefore, to better understand if rAd-p53 SCH 58500 exhibits antitumor biological activity in patients, it is important to know if the expression of the proapoptotic/apoptotic and cell cycle regulated genes such as p21/WAF1, bax, mdm-2, and survivin are modulated following the administration of rAd-p53 SCH 58500.

Typical preclinical methods for investigating the expression of p53 and its regulated genes after p53 gene therapy involve assessing the extent of protein phosphorylation or changes in protein levels, or using Northern blots to assess relative mRNA levels. Although a relatively straightforward endeavor when samples are obtained from tumor cell lines or xenografts in mice, human clinical samples are usually available in very limited quantities and with few or no proper controls. Limited human tissue specimens must be subjected to a battery of very sensitive tests to evaluate the activity. For this reason, prior to analyzing subject samples, we developed and validated quantitative PCR (QPCR) and quantitative RT-PCR (QRT-PCR) assays using various xenograft tumor models.[26] Since the presence of endogenous human p53 and p21 proteins causes interference in many protein-based assays, and because such methods are relatively insensitive for quantifying specific proteins, we also applied QRT-PCR assay as an alternative tool to quantify p53 gene expression at mRNA level, instead of as protein.

Results from a phase I/II trial of rAd-p53 SCH 58500 gene therapy in recurrent ovarian cancer were recently published.[6,7] The primary objective of these studies was to evaluate safety. We were limited in our ability to obtain biological samples, which require invasive procedures, for a more detailed evaluation. To obtain tumor biopsies and peritoneal aspirates during multiple cycle administration, we enrolled an additional five subjects to the trial. Safety and clinical activities of rAd-p53 SCH 58500 have been discussed elsewhere;[6,7] therefore, the present study focused on the assessment of p53 biological activity and the levels of p53 transgene expression possible in recurrent ovarian cancer subjects receiving multiple cycles of daily dosing of rAd-p53 SCH 58500.

Materials and methods

Clinical preparations of rAd-p53 SCH 58500

rAd-p53 SCH 58500 is a replication-deficient recombinant human adenovirus type 5 encoding the human $p53^{wt}$ gene under transcriptional control of the cytomegalovirus promoter. The construction, production, and purification via column chromatography of rAd-p53 SCH 58500 have been previously described.[27,28] rAd-p53 SCH 58500 was administered on the basis of adenoviral particle number, which was determined via an OD260 nm/SDS method.[29]

Trial subject characteristics

Five female subjects with peritoneal carcinoma with pathologically confirmed recurrent ovarian cancer were entered into the study in the bioanalytical subcohort. Entry criteria included peritoneal fluid positive for tumor cells and tumor accessible for laparoscopic or percutaneous biopsy. All trial subjects must have tumors confirmed to have a p53 mutation as determined by cDNA sequencing.[30]

Study design and sample collection

Trial subjects were consented to receive multiple dose cycles of rAd-p53 SCH 58500 via intraperitoneal administration. For trial subjects with pre-existing peritoneal fluid of a clinically significant amount, as much peritoneal fluid as possible was drained prior to administration of the first dose of rAd-p53 SCH 58500. In all subjects, 7.5×10^{13} particles of rAd-p53 SCH 58500 was administered intraperitoneally in 250 mL of saline on each of five consecutive days during each cycle of treatment.[7] Each cycle consisted of the five daily administrations of SCH 58500 followed by a 3-week 'rest' interval prior to the next

cycle. Subjects were dosed with rAd-p53 SCH 58500 alone during the first cycle and were dosed in combination with gemcitabine in the four subsequent cycles. For cycles 2 and 3, 800 mg/m^2 gemcitabine was delivered intravenously on days 1, 8, and 15. Peritoneal aspirate was scheduled for collection via paracentesis prior to rAd-p53 SCH 58500 administration on day 1 of each cycle and on day 5 prior to administration of the fifth dose of each cycle. Cell pellets from peritoneal aspirate were obtained and washed with PBS. Approximately, 1.0×10^6–1.0×10^7 cells from each subject were analyzed by QPCR and QRT-PCR assays, while 2.0×10^4 cells from each subject were analyzed via *in situ* PCR. Tumor biopsies were collected via laparoscopy or percutaneously predose on day 1 and after the fourth dose of the first and third cycles (prior to the fifth dose) on day 5. Biopsy samples consisted of approximately 10–100 mg of tissue. Samples were snap frozen and kept at −80°C until use. rAd–p53 SCH 58500 was administered on an outpatient basis. The subjects were kept under observation for at least 2 hours after every dose, or until the subject had recovered from any toxicity.

Quantification of expression of rAd-p53 SCH 58500, p21/WAF1, bax, caspase-3, survivin, mdm-2, and viral DNA

QPCR and QRT-PCR were employed to quantify rAd-p53 SCH 58500 viral DNA and gene expression using the Sequence Detector 7700 (Taqman®, Applied Biosystems, Foster City, CA) as reported previously.[26] The GAPDH housekeeping gene was used as an internal control to assess the quality of assay samples and to normalize results. No results were reported if GAPDH DNA or RNA was less than 1000 copies per PCR reaction. rAd-p53 SCH 58500 DNA was quantified against a standard curve constructed from viral DNA extracted from purified rAd-p53 SCH 58500 virus (Qiagen, Valencia, CA). Two types of standard curves were used to quantify gene expression in this study. cRNA[26] was used to quantify p53, p21/WAF1, bax, mdm-2, and GAPDH gene expression. A standard created from serially diluted RNA extracted from rAd-p53 SCH 58500-infected A549 cells was used to quantify caspase-3 and survivin expression. Gene expression results were expressed as the number of copies of the gene per 1000 copies of GAPDH (eg, when the cRNA standard was applied). In the case of caspase-3 and survivin, expression results were expressed as molecular equivalents (MEQ) per 1000 copies of GAPDH (eg, when the serially diluted total RNA standard was applied). MEQ is an arbitrarily assigned number based on serially diluted total RNA from rAd-p53 SCH 58500-infected cells. The sequences of the oligonucleotide primers and probes are shown in Table 1. The same primer sets and probes were used to perform PCR and RT-PCR for the p53 transgene. This set of primers and probe do not recognize the endogenous p53 gene sequence, and therefore only amplify rAd-p53 SCH 58500.[26,27]

Bioassay for adenovirus serum neutralizing factors

HEK 293 cells were plated onto collagen-I-coated 96-well plates (BioCoat, Fort Washington, PA) and incubated at 37°C in a 5% CO_2 incubator for 3 hours prior to sample addition. Sera for analysis were serially diluted two-fold

Table 1 Sequence of oligonucleotide primers and probes used in Q PCR and RT–PCR

Target gene	Primer/probe	Sequence	PCR product size
p53	Forward primer	5′-AACGGTACTCCGCCACC-3′	94
	Reverse primer	5′-CGTGTCACCGTCGTGGA-3′	
	Probe[a]	5′-CAGCTGCTCGAGAGGTTTTCCGATCC-3′	
Bax	Forward primer	5′-TCCCCCCGAGAGGTCTTTT-3′	68
	Reverse primer	5′-CGGCCCCAGTTGAAGTTG-3′	
	Probe[a]	5′-TCAGAAAACATGTCAGCTGCCACTCGG-3′	
p21/WAF1	Forward primer	5′-TGGAGACTCTCAGGGTCGAAA-3′	65
	Reverse primer	5′-GGCGTTTGGAGTGGTAGAAATC-3′	
	Probe[a]	5′-CGGCGGCAGACCAGCATGAC-3′	
Survivin	Forward primer	5′-TGCCCCGACGTTGCC-3′	69
	Reverse primer	5′-CAGTTCTTGAATGTAGAGATGCGGT-3′	
	Probe[a]	5′-CCTGGCAGCCCTTTCTCAAGGACC-3′	
Caspase-3	Forward primer	5′-TGCGCTGCTCTGCCTTCT-3′	141
	Reverse primer	5′-CCATGGGTAGCAGCTCCTTC-3′	
	Probe[a]	5′-AGCTTCTTCATTTGTGTGCTCCGCTTTCA-3′	
Mdm-2	Forward primer	5′-TTACCCAGGCTGGAGTGCAG-3′	92
	Reverse primer	5′-GAGAATGGTGCGAACCCG-3′	
	Probe[a]	5′-TGGCTCACTGCAAGCTCTGCCCTC-3′	
GAPDH	Forward primer	5′-GAAGGTGAAGGTCGGAGTC-3′	226
	Reverse primer	5′-GAAGATGGTGATGGGATTTC-3′	
	Probe[a]	5′-CAAGCTTCCCGTTCTCAGCC-3′	

[a]All probes were labeled with FAM at the 5′ end as the reporter and TAMRA at the 3′ end as the quencher.

and placed onto the analysis plate(s). rAd-p53 SCH 58500 was then added so that there were 25 virus particles per cell. Assay plates were incubated for 72 hours. The plated cells were then fixed using a 1:1 (v/v) acetone:methanol solution. Fixed cells were stained for the presence of intracellular adenovirus hexon protein using a rabbit polyclonal anti-hexon antibody that had been raised against rAd-p53 SCH 58500 and a secondary FITC-labeled anti-rabbit Ig antibody (Chemicon, Temecula, CA). The fluorescence in each well was read using a CytoFluor II multiwell plate reader (Waters, Milford, MA). For each sample, the dilution factor was plotted *versus* the fluorescence intensity. Titer was then calculated by determining the inverse of the dilution factor that resulted in 50% of the maximum fluorescence intensity. The final result, the neutralizing anti-rAd-p53 SCH 58500 antibody titer, was expressed as the number of adenoviral particles neutralized per 1 mL of serum, and was calculated from a positive control curve created using rAd-p53 SCH 58500.

In situ *PCR for rAd-p53 SCH 58500 DNA in peritoneal aspirate and tumor biopsies*

To assess gene delivery to tumor and surrounding tissues, formalin-fixed paraffin-embedded tissue sections from each subject's tumor biopsy samples were analyzed using the *in situ* PCR assay as described previously.[4,7] To assess gene delivery into cells found in the peritoneal aspirates, cells were pelleted from each subject's peritoneal fluid at 1000 rpm (approximately 300 *g*) for 5 minutes. After depletion of erythrocytes, approximately 2.0×10^4 cells were centrifuged onto *in situ* PCR slides using a Cytospin 3 (Shandon, Pittsburgh, PA) at 600 rpm for 10 minutes. After air-drying, the slides were fixed in 10% (v/v) formalin for 10 minutes and then dehydrated through a series of graded alcohol incubations. The slides were then processed as previously described with minor modifications.[4] The Proteinase K digestion step was not performed on cells isolated from peritoneal fluid. Dinitrophenyl (DNP) labeled rAd-p53 SCH 58500 specific primers were used to amplify specifically rAd-p53 SCH 58500 but not endogenous p53. The sequence for the forward primer was

5′-CCACTGCTTACTGGCTTATCGAAAT-3′

The sequence for the reverse primer was

5′-CGTGTCACCGTCGTGGA-3′

A rabbit anti-DNP primary antibody (Zymed, San Francisco, CA) and an anti-rabbit IgG antibody conjugated with peroxidase (Vector, Burlingame, CA) were used to detect the PCR product. Positive rAd-p53 SCH 58500 viral DNA was visualized using a 3-amino-9-ethyl carbazole (AEC) substrate (Dako Corporation, Carpinteria, CA), after which samples were counterstained with hematoxylin.

Apoptosis analysis using laser scanning cytometry

The laser scanning cytometry (LSC) method has been previously described.[31] Briefly, blocks were cut into 5 μm sections and mounted on glass slides. The tissues were stained for apoptosis using a modified fluorescence TUNEL assay and stained for nuclear identification using 0.001% (w/v) propidium iodide. Slides were scanned using a CompuCyte brand LSC™. The fluorescein-dUTP incorporated into nicked DNA ends was excited by a 488-nm argon laser interrogation. A total of 12 sections were taken from each tumor block for laser scanning cytometry analysis. These sections were analyzed on six different analysis days (two sections per analysis day) to account for both sample variability and instrument variability. Qualification studies for the assay method had previously determined that the single greatest source of variability in the method, after sampling, was inter-day scanning (analysis day). On each analysis day for each sample, one slide was used for apoptosis staining (TUNEL reaction) and one as the negative control. The negative control consisted of the fluorescein-dUTP reaction performed in the absence of the labeling enzyme TdT. On each analysis day, the percentage of apoptotic nuclei per total nuclei scanned was calculated. Daily percentages were averaged across the 6 days to determine the mean percentage of apoptosis within the 'tumor'. Standard error of the mean was calculated based on the per cent daily variation.

Results

Sample collection

Peritoneal fluid samples successfully collected for analysis are listed in Table 2. The frequency of laparoscopic/percutaneous or fine needle aspiration biopsies was limited because of ethical concerns based upon the invasive nature of these procedures and based on the trial subject health conditions at the time of collection. Pre- and postdose biopsies were collected from all trial subjects from Cycle 1. However, a Cycle 3 biopsy sample was only able to be collected from one trial subject, subject 53. Peritoneal aspirate was collected on Day 1, prior to the first dose in a cycle, and on Day 5th, approximately 24 hours after the fourth dose but prior to administration of the fifth dose administration, for each cycle with the exception of two samples. Owing to the health of the subject, Cycle 2 postdose sample from subject 50 was collected on Day 7 (2 days after the fifth dose) and Cycle 4 postdose sample from subject 52 was collected on Day 8 (3 days after the fifth dose).

Gene transfer and expression from rAd-p53 SCH 58500 in tumor biopsy samples

Gene transfer and expression were assessed using QPCR and QRT-PCR as described. We detected rAd-p53 SCH 58500 DNA in five of five (Fig 1a) and RNA in four of five (Fig 1b) subject Cycle 1/Day 5 biopsy samples. Neither rAd-p53 SCH 58500 DNA nor RNA was detected in any of the predose biopsy samples (Cycle 1/Day 1; data not shown). Samples collected from subject 53 showed no detectable p53 transgene RNA in either the Cycle 1/Day 5 postdose or the Cycle 3/Day 5 postdose

Tabl 2 Peritoneal fluid sample collection summary

Subject no. (Age, stage of cancer at original diagnosis)	No. of cycles completed	Collection of peritoneal fluid							
		Cycle 1		Cycle 2		Cycle 3		Cycle 4	
		Pre[a]	Post[b]	Pre	Post	Pre	Post	Pre	Post
49 (42, IIIC)	3	NE	Y	NE	Y	Y	Y	NA	NA
50 (53, IIC)	2	NE	Y	NE	Y[c]	NA	NA	NA	NA
52 (63, IIIC)	4	Y	Y	Y	Y	NE	Y	Y	Y[d]
53 (66, IIIC)	3	Y	Y	NE	NE	NE	Y	NA	NA
54 (48, IIIC)	3	Y	Y	Y	Y	Y	Y	NA	NA

[a]Preperitoneal fluid was collected prior to the first dose of each cycle.
[b]Postperitoneal fluid was collected on Day 5 of each cycle, after the fourth dose of rAd-p53 SCH 58500 but prior to the fifth dose.
[c]This sample was collected on Day 8, 3 days after the fifth dose.
[d]This sample was collected on Day 7, 2 days after the fifth dose.
NA: No rAd-p53 SCH 58500 was administered during this cycle; NE: No evaluable sample was collected; Y: An evaluable sample was collected.

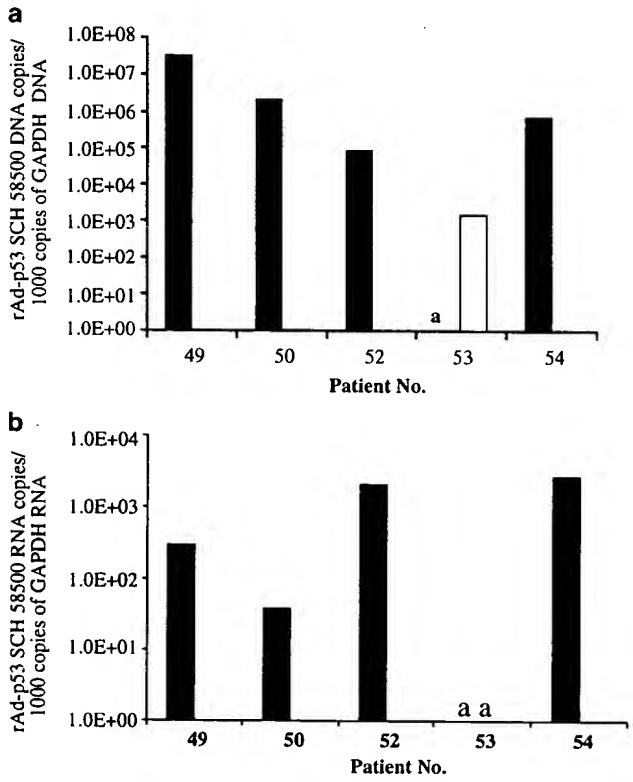

Figure 1 Quantification of rAd-p53 SCH 58500 gene delivery and expression in tumor samples. Panel **a**: rAd-p53 SCH 58500 gene transfer DNA levels. Panel **b**: rAd-p53 SCH 58500 gene expression RNA levels. Cycle 1/Day 5, closed bar, Cycle 3/Day 5, open bar. a: below quantification.

tumor samples. Although rAd-p53 SCH 58500 DNA was detected below the limit of quantification (10 copies per PCR reaction) for subject 53's Cycle 1/Day 5 postdose and Cycle 3/Day 1 predose samples, the levels of rAd-p53 SCH 58500 DNA were found to be elevated in the Cycle 3/Day 5 biopsy sample (Fig 1a).

Gene transfer and expression of rAd-p53 SCH 58500 in peritoneal aspirates

rAd-p53 SCH 58500 DNA (Fig 2a) and RNA (Fig 2b) from postdose peritoneal aspirates for each cycle were measured using QPCR and QRT-PCR. As shown in Figure 2b, subjects 53 and 54 had elevated levels of rAd-p53 SCH 58500 RNA in samples collected from Cycle 3/Day 5, as compared to that from the previous cycles. In subject 52, we observed an increase in the amount of rAd-p53 SCH 58500 RNA in Cycle 2 with the RNA amount gradually decreasing over Cycles 3 and 4. By contrast, decreasing amounts of RNA were observed in these dose cycles in samples from subjects 49 and 50. All postdose peritoneal aspirates we examined contained detectable levels of rAd-p53 SCH 58500 RNA with the exception of two samples. Interestingly, these two samples were not collected on Day 5 as per the protocol, but instead, they were collected on Cycle 2/Day 8 for subject 50 and on Cycle 4/Day 7 in the case of subject 52. rAd-p53 SCH 58500 DNA was consistently detected at high levels in cells collected from all cycles (Fig 2a). In addition, rAd-p53 SCH 58500 DNA remained detectable in cells collected from peritoneal aspirates between dosing cycles, whereas RNA levels dropped below our limit of quantification (10 copies per PCR reaction) in peritoneal cells collected on Day 1 immediately before the next cycle of dosing. A representative example of this observation is shown in Figure 3 and contains data from subject 54. These data may imply that the duration of RNA is much shorter than for DNA. No rAd-p53 SCH 58500 DNA or RNA was detected in any of the samples collected at the predose Cycle 1 time point (data not shown).

Serum anti-adenovirus neutralizing factors

Positive serum antiadenovirus neutralization activity (SNF) was observed in all subjects prior to treatment;

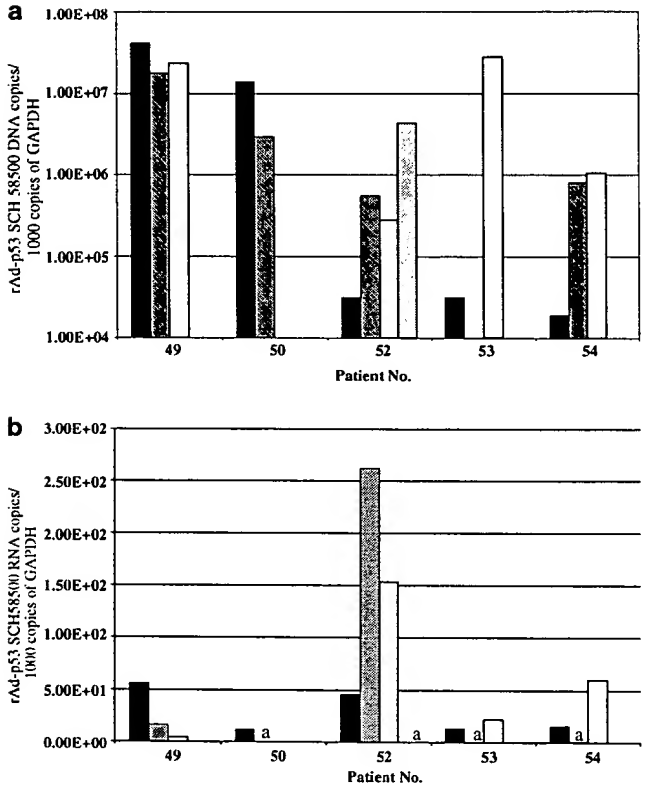

Figure 2 rAd-p53 SCH 58500 DNA (a) and RNA (b) levels in postdose peritoneal aspirates. C1: Cycle 1; C2: Cycle 2; C3: Cycle 3; C4: Cycle 4. Black bar: C1/D5; gray bar: C2/D5; white bar: C3/D5; light gray bar: C4/D7. a: below quantification level.

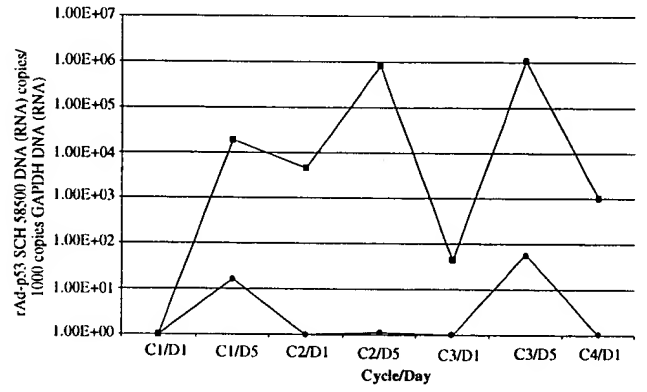

Figure 3 rAd-p53 SCH 58500 DNA and RNA in Various Pre- and postdose peritoneal aspirates collected from subject 54. ■: DNA. : RNA.

the baseline level of neutralization capacity ranged between 1.5×10^8 and 7.0×10^9 virus particles neutralized per milliliter of serum (Table 3). Neutralization capacity increased in subjects 49, 50, 52, and 53 after each dosing cycle; however, SNF titers dropped to near baseline during the 3 weeks between dosing for all subjects, except in the case of subject 54. Subject 54 had the lowest SNF titers prior to dosing in Cycle 1, and SNF titers increased over the course of the three dosing cycles without dropping back to the predosing baseline value.

p53 biological activity

To understand whether the level of gene transfer delivered in these subjects was sufficient to induce p53 transcriptional activities, we investigated the expression levels of the p53-mediated genes, p21/WAF1, bax, and mdm-2, and of genes involved in the apoptotic pathway, caspase-3, and survivin, using QRT-PCR. rAd-p53 SCH 58500 mediated p21/WAF1 upregulation was observed in the Cycle 1/Day 5 tumor samples from all subjects who received four doses of rAd-p53 SCH 58500 (Table 4), with the exception of the Cycle 1/Day 5 tumor sample from subject 53. We observed a greater than 10-fold increase in p21/WAF1 expression levels in tumor samples from subjects who had detectable rAd-p53 SCH 58500 RNA. Consistent with the high levels of rAd-p53 SCH 58500 RNA detected in tumor samples from subjects 52 and 54, we observed a greater increase in the expression level of p21/WAF1 in these same two subjects as well. The Cycle 1/Day 5 tumor samples from subjects 52 and 54 had a greater than 100- and 30-fold increase in p21/WAF1 expression over the Cycle 1/Day 1 predose tumor samples, respectively.

We also investigated the change in proapoptotic gene expression after rAd-p53 SCH 58500 administration (Table 4). rAd-p53 SCH 58500 mediated upregulation of bax expression was observed in four of five subject Cycle 1/Day 5 tumor samples, and ranged from a three- to a 27-fold increase. The Cycle 1/Day 5 tumor samples from subjects 49 and 50 showed no increases in caspase-3 expression. Subjects 52 and 54 were both observed to have a greater than four-fold increase in caspase-3 expression levels in their Cycle 1/Day 5 tumor samples (Table 4). Consistent with the lack of detectable p53 transgene expression (Fig 1b), we observed no changes in p21/WAF1, bax, or caspase-3 expression in subject 53's Cycle 1/Day 5 tumor biopsy sample. Survivin expression decreased in three of five subject tumor samples, ranging from three- to nine-fold. Upregulation of mdm-2 was observed in two out of five Cycle 1/Day 5 tumor samples from subjects with detectable p53 transgene expression (Table 4). Interestingly, no detectable mdm-2 expression was observed in subject 52's predose tumor biopsy sample.

In contrast to biopsy samples, there were no consistent changes in the RNA levels of bax, caspase-3, mdm-2, or survivin in the peritoneal aspirates (data not shown). We did observe consistent upregulation of p21/WAF1 gene expression in all but one postdose peritoneal aspirate. Since we were more consistently able to collect peritoneal aspirates, we were able to evaluate whether rAd-p53 SCH 58500 could upregulate p21/WAF1 in a multiple dosing regimen using data from the pre- and postdose peritoneal aspirates collected in each cycle. As shown in Figure 4,

Table 3 Detection of Serum Anti-Adenoviral Neutralizing Factors in Clinical Trial Subjects

Days after first administration (Cycle no.)	Antiadenovirus neutralizing titer (No. of viral particles neutralized per mL serum)				
	Subject 49	Subject 50	Subject 52	Subject 53	Subject 54
1 (Cycle 1)	1.25×10^9	6.78×10^9	6.60×10^9	4.99×10^9	1.54×10^8
3	1.69×10^9	3.50×10^{11}	3.56×10^8	1.17×10^9	NA
7	NA	7.47×10^{10}	2.24×10^9	3.08×10^9	NA
14	5.62×10^9	2.15×10^{11}	4.69×10^{10}	2.88×10^{10}	2.02×10^8
21	1.85×10^{10}	NA	NA	3.91×10^{10}	3.32×10^8
28 (Cycle 2)	2.68×10^9	1.71×10^9	1.94×10^9	2.31×10^9	8.78×10^9
35	3.11×10^9	NA	NA	NA	1.36×10^9
48	NA	1.36×10^{11}	NA	7.23×10^{10}	NA
49	1.83×10^{10}	NA	NA	NA	2.18×10^9
56 (Cycle 3)	NA	NA	9.70×10^8	4.09×10^9	NA
62	NA	1.52×10^{10}	NA	4.92×10^{10}	NA
63 (Cycle 3)	4.96×10^9	—[a]	3.76×10^{10}	NA	2.90×10^9
70	5.48×10^9	—	4.42×10^{10}	2.26×10^{10}	6.24×10^9
78	1.46×10^9	—	4.43×10^9	7.05×10^{10}	NA
91	4.74×10^9	—	NA	NA	5.94×10^9

Serum was collected prior to the first dose and after each cycle of rAd-p53 SCH 58500 administration.
Gray shading indicates the first day of SCH 58500 administration for each cycle. On the first dose of each cycle, serum was sampled prior to rAd-p53 SCH 58500 administration.
[a]Subject stopped receiving rAd-p53 SCH 58500; NA: not applicable.

Table 4 Changes in gene expression as compared to Cycle 1/Day 1 pre-dose samples

Subject no.	Fold change in expression level					rAd-p53 SCH 58500 RNA (copies/1000 MEQ of GAPDH)
	Bax	Capase-3	Mdm-2	p21/WAF1	Survivin	
49	↑3 ×[a]	NC	↑4200 ×	↑10 ×	↓9 ×[b]	295
50	↑3 ×	NC	NC	↑23 ×	NC	38
52	↑23 ×	↑4 ×	BQL[c]	↑138 ×	↓3 ×	2100
53	NC[d]	NC	NC	NC	↓3 ×	BQL
54	↑27 ×	↑10x	↑30 ×	↑30 ×	[1]NC	2720

[a]↑: indicates an increase in expression level.
[b]↓: indicates a decrease in expression level.
[c]BQL: below quantification level, ie, 10 copies per PCR reaction.
[d]NC: No change, defined as less than or equal to a two-fold change.

upregulation of p21/WAF1 was observed not only in the Cycle 1 peritoneal aspirates, but also in peritoneal aspirates from subsequent cycles.

Gene delivery localization

In situ PCR was utilized to localize rAd-p53 SCH 58500 viral DNA in cells collected from peritoneal aspirates and tumor biopsy samples. Positive rAd–p53 SCH 58500 DNA signal was mainly found in peritoneal polymorphonuclear neutrophils (PMNs) (Fig 5, panels c and d). Our observations also indicate that PMN numbers increased significantly in postdose peritoneal aspirates (Fig 5, panels a and b). Tumor cells were very difficult to identify in the peritoneal aspirates. Predose peritoneal aspirates (Fig 5, panel e) did not contain any positive signal for rAd-p53 SCH 58500. rAd-p53 SCH 58500 DNA sequence was detected in tumor biopsy samples following rAd-p53 SCH 58500 dosing (Fig 6, panel b). Positive rAd-p53 SCH 58500 DNA signal was detected in epithelial cells, stromal cells, and tumor cells. No rAd-p53 SCH 58500 DNA signal was observed in any of the predose tumor samples (Fig 6a).

Apoptosis analysis

Pre- and postdose tumor biopsies from subjects 49, 50, and 52 were made available for the LSC/TUNEL analysis. This analysis was quantified over six different tissue sections, with an average total of 50,000 nuclei per tumor section having been scanned. We observed a trend in samples from three subjects of increased apoptosis from pre- to postdose; however, the difference could not be resolved at $P < .05$. For example, subject 50 changed

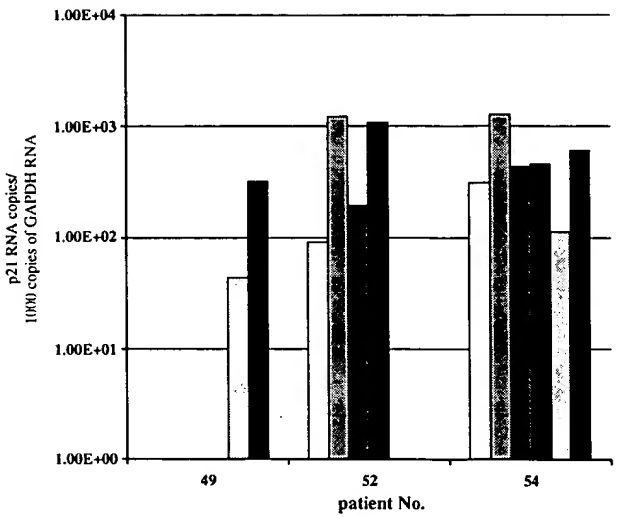

Figure 4 Changes in p21/WAF1 gene expression in peritoneal aspirates. Pre- and postdose samples collected from the same cycle are summarized for comparison. □: C1/D1, ▨: C1/D5, ■: C2/D1, ■: C2/D5, □: C3/D1, ■: C3/D5.

from an apoptosis level of 13.5±5.9% on Cycle 1/Day 1 to 15.5±4.6% apoptosis positive signal on Cycle 1/Day 5. Subject 52 biopsy samples were found to have an apoptosis measurement of 8.5±3.2% on Cycle 1/Day1, and that increased to 11.0±3.0% on Cycle 1/Day 5. The mean apoptosis value was determined by averaging six different sections within each tumor as described in Materials and methods. A false-color bit-map analysis of a representative set of scans for subject 52 shows that apoptosis was present on the periphery of the section at Cycle 1/Day 1, and that after 4 days (Cycle 1/Day 5), apoptosis was observed within the interior of tumor section (Fig 7). Furthermore, intermittent check sections were stained using conventional ApopTag™ immunohistochemistry staining; these sections confirmed the levels of apoptosis observed in the LSC scans (data not shown).

Discussion

In this study, we applied several bioanalytical methodologies to analyze biopsy and ascitic samples with the aim of assessing gene transfer efficiency in a multiple dose regimen of rAd-p53 SCH58500. We also sought to investigate what biological activity resulted from p53 gene expression after rAd-p53 SCH 58500 treatment. One of the major hurdles we encountered was the difficulty in collecting sufficient amounts and numbers of biopsy samples from subjects at an appropriate time point for each specific evaluation. This limits the amount of useful information available to understand the impact of cancer gene therapy in humans. However, we were able to conclude that (1) gene transfer was not abrogated by the presence of antiadenovirus neutralizing factors, and (2) the levels of rAd-p53 SCH 58500 delivered into tumor in human subjects were sufficient to induce p53-mediated transcriptional activity.

To investigate whether the expression of p53 affected the expression of p53-regulated genes after rAd-p53 SCH 58500 administration, one would prefer to assess the extent of protein phosphorylation or changes in protein levels. However, the interference from endogenous proteins (eg, p21) and the limitation in the amount of clinical sample made it difficult to attribute the changes to exogenously introduced p53 gene. In addition, the absence of an adenovirus control made it more difficult to assess p53 specific activities independent of any effects because of the adenovirus vector itself. For these reasons, we had previously conducted preclinical studies with appropriate treatment control groups to demonstrate that QRT-PCR and PCR assays are feasible alternatives to evaluate the changes in the expression of p53-mediated genes.[26]

To examine if delivered $p53^{wt}$ gene could result in transactivating its downstream genes, we investigated p21, bax, mdm2, caspase-3, and survivin gene expression levels and their changes with dosing. The decreased levels of survivin observed in three of five subjects' tumor biopsies are inconsistent with a previous study[32] that demonstrated when $p53^{wt}$ was introduced into 2774qw1 cells, survivin expression was repressed while p21/WAF1 expression increased. Although the significance of this observation is not clear, it has been suggested that survivin may play a role in the p53-mediated apoptotic pathway.[32] We found that the only sample that did not show elevation of p21/WAF1 and bax expression was tumor from subject 53. However, subject 53's tumor did not have detectable p53 transgene expression.

Together these observations strongly suggest that the upregulation of p21/WAF1 and bax expression (Table 4) were mediated by rAd-p53 SCH 58500. Indeed, rAd-p53 SCH 58500-mediated upregulation of p21/WAF1 has been documented in trials conducted in small-cell lung cancer and bladder cancer.[4,33] Since no subjects were treated with a rAd-control vector, we could not rule out the possibility of a vector effect. Notably, we did not observe upregulation of p21/WAF1 or bax gene expression in a control group of animals treated with a rAd vector containing no transgene in a pilot study we performed.[26] Importantly, no chemotherapeutic agent was administered during the cycle. This indicates that this observation was not a result of chemotherapy. Since biopsies were collected on day 5, 4 days after the first dose and 24 hours after the fourth dose of rAd-p53 SCH 58500, PMN had significantly increased in peritoneal fluid by this time point. Therefore, we cannot rule out the possibility that the changes in gene expression are because of infiltrating cells that have migrated to tumor sites in response to the rAd-p53 SCH 58500 administration. In peritoneal aspirates, consistent upregulation of p21 was observed; however, changes in the expression levels of the apoptotic-related genes, bax, caspase-3, and survivin were inconsistent among subjects.

We were unable to identify tumor cells in the peritoneal aspirates from the Day 5 time points (Fig 5a and b). The

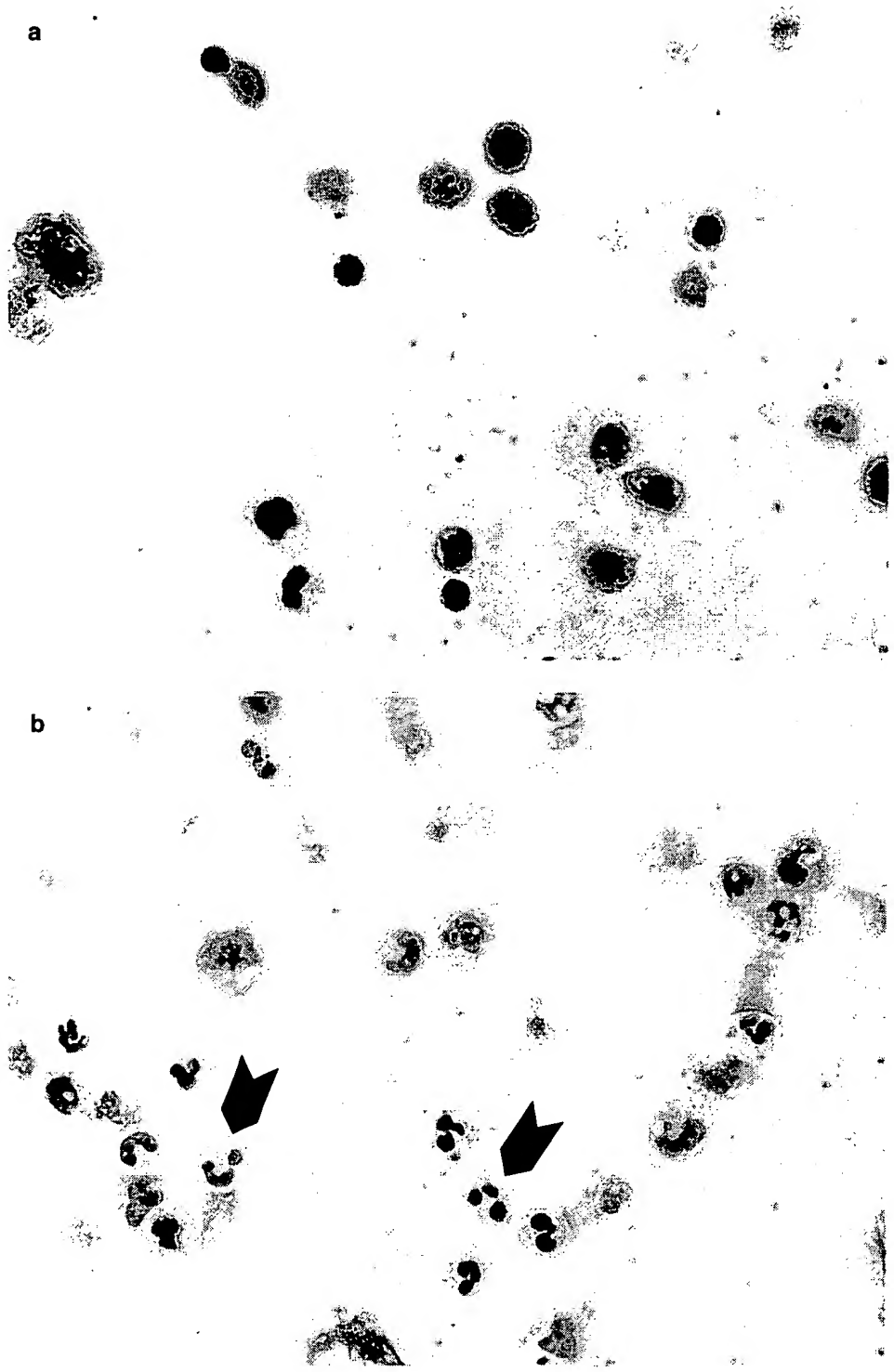

Figure 5 *In situ* PCR Localization of rAd-p53 SCH 58500 DNA in peritoneal aspirates. cells from peritoneal aspirates were collected on Day 1 (prior to the first dose) and Day 5 (prior to the fifth dose) of each cycle. H&E staining (panels a and b) shows that PMNs with multilobed nuclear characteristics (arrow head) significantly increased in numbers in postdose peritoneal aspirates (panel a, Cycle 1/Day 1, × 100, panel b, Cycle 1/Day 5, × 100). Panels c and d show the results of the *in situ* PCR assay for rAd-p53 SCH 58500: DNP-labeled primers were used to amplify rAd-p53 SCH 58500 DNA *in situ*. Brown positive rAd-p53 SCH 58500 DNA staining was observed in the Day 5 postdose samples from Cycle 1 (panel c, × 1000) and Cycle 2 (panel d, × 100) but not in the Cycle 1/Day 1 predose sample (panel e, × 100). Arrows indicate positive rAd-p53 SCH 58500 DNA signal (brown color). Dotted arrows indicate negative rAd-p53 SCH 58500 DNA signal (blue color).

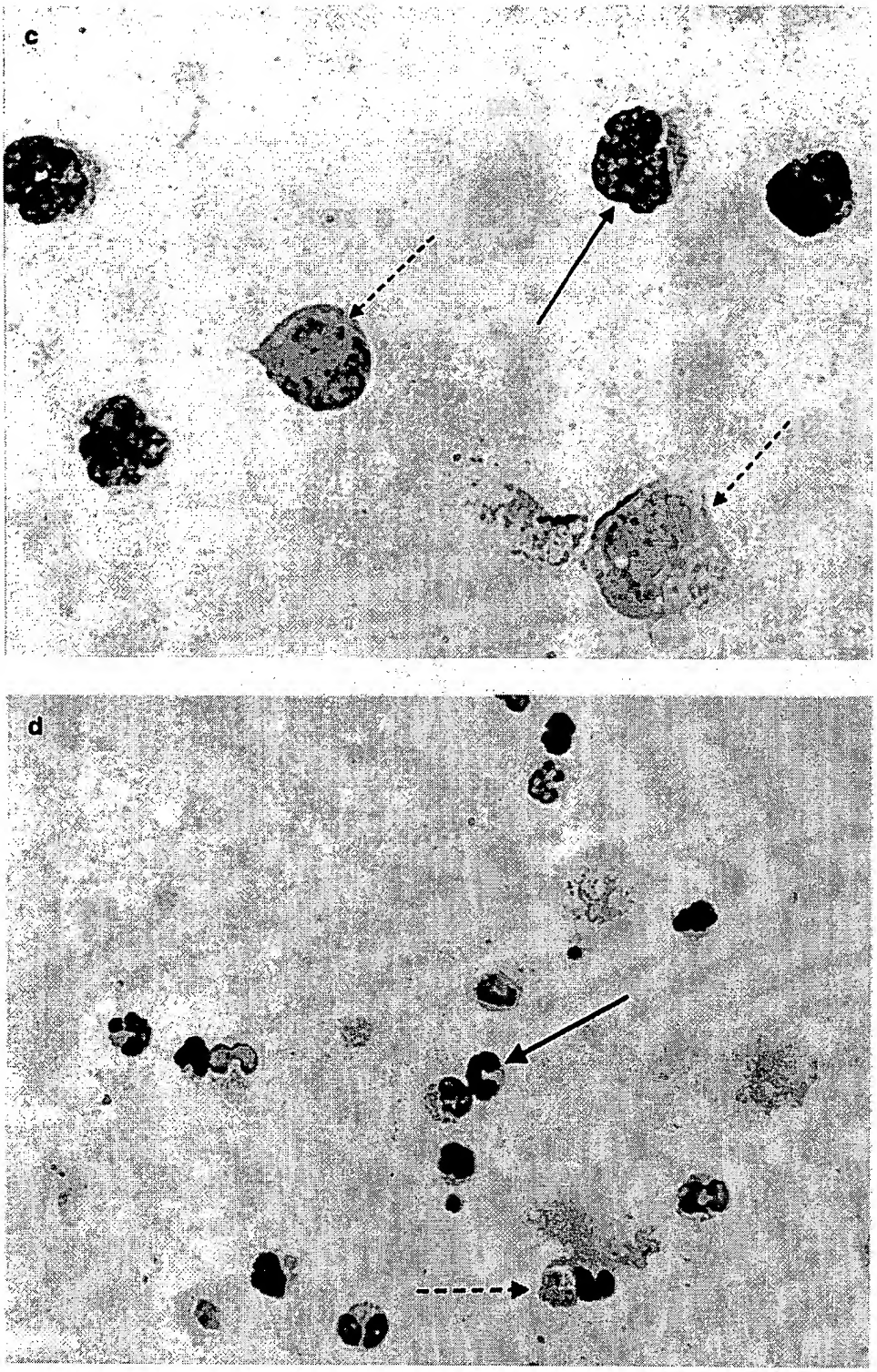

Figure 5 *Continued.*

failure to identify tumor cells in peritoneal aspirate may also be because of the timing of samples. The Day 5 time point is long enough to allow tumor cells to complete the apoptotic process if triggered to do so by expression of p53 from the administered rAd-p53 SCH 58500. Therefore, the Day 5 results likely represent the expression levels primarily in PMN cells. In order to evaluate peritoneal tumor cell responses to rAd-p53 SCH 58500 treatment, we may need to develop a different method so as to isolate the relatively few tumor cells from the more abundant nontumor cells in any future studies.

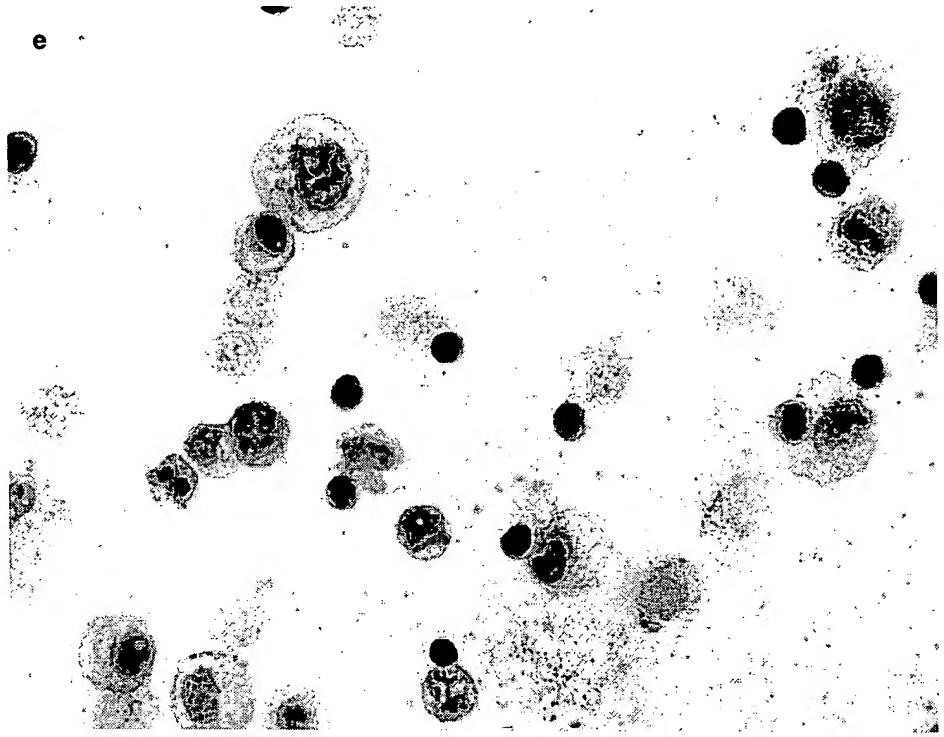

Figure 5 *Continued.*

Although the roles of bax, caspase-3, and survivin genes in apoptosis are well established, we cannot confirm that the changes in bax, caspase-3, and survivin gene expression levels we observed would in fact result in a favorable apoptotic response in the tumor cells of our trial subjects. We have previously shown in preclinical studies that LSC can be used to resolve rAd-p53 SCH 58500-induced apoptosis in human xenograft tumors.[31] Using the same methodology, we wanted to see if we could observe a significant increase in rAd-p53 SCH 58500-mediated apoptosis in tumor biopsies derived from subjects on study. Although some investigators have reported an increase in apoptotic tumor cells after treatment with rAd-p53 and cisplatin[8] in patients with nonsmall-cell lung cancer, we were unable to establish that the increases seen were statistically significant. We did observe a clear trend of increasing apoptosis in the tumor biopsy sections for subjects between the predose and postfourth dose time points in a cycle. The lack of statistical significance may be because of the small number of trial subject tumor tissue blocks available, and/or the variation between trial subjects. Sample timing may also provide one plausible explanation for the inability to observe a statistical increase in apoptosis. It has been suggested that the apoptotic process is complete within several hours.[34] In this trial, samples were collected 24 hours after the fourth of the five consecutive daily administrations within a cycle, a time that may have caused us to underestimate the degree of the apoptosis induced by rAd-p53 SCH 58500.

In addition to evaluating p53 transcriptional activity, another major goal of this study was to investigate the impact of multiple administration cycles on gene transfer and expression. QPCR and QRT-PCR results from the peritoneal aspirates and a limited number of tumor biopsies indicate that it is possible to deliver the p53 gene into cells even in later dosing cycles. Indeed, the elevation of rAd-p53 SCH 58500 DNA (Fig 1a and Fig 2a) and RNA (Fig 2b) detected in the later cycles indicates that the higher levels of transgene expression can be achieved with repeated intraperitoneal dosing even with increased antiadenovirus neutralizing factor (SNF) in all trial subjects. As expected, SNF titers increased in all subjects during the course of treatment; however, with the exception of one subject, there was a rise and fall pattern between dosing cycles. SNF titers had dropped to baseline on the day of initiation of a subsequent cycle of rAd-p53 SCH 58500. Although anti-adenovirus neutralizing factors found in the peritoneal aspirates were not measured in this study, it has been documented in a previous study[35] that similar titers were observed in both serum and peritoneal fluid from ovarian cancer patients. Although all subjects in this study had pre-existing anti-adenovirus SNF, gene transfer was detected in all subjects and there was no correlation between the level of p53 gene transfer and SNF titer. Similar results have been reported for a mesothelioma phase I clinical trial where a rAd5 carrying a suicide gene was administered to trial subjects intrapleurally.[36] One possible explanation for this is the dose level (3.0×10^{14} particles) given to the subjects prior to sample collection. The dose amount may exceed the antiadenovirus SNF neutralizing capacity.

In situ PCR analysis revealed that we were able to deliver rAd-p53 SCH 58500 to tumor cells (Fig 6) in a

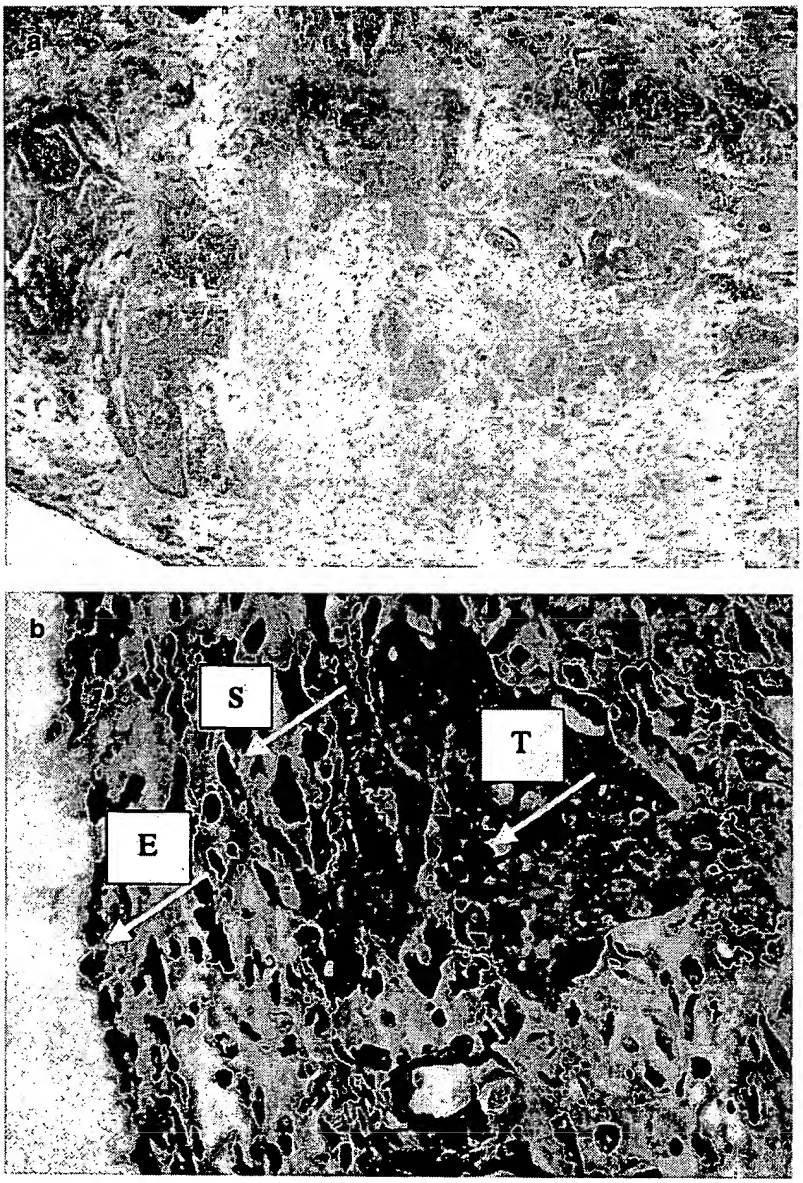

Figure 6 *In situ* PCR localization of rAd-p53 SCH 58500 DNA in tumor biopsy samples. Tumor biopsies from subject 50 prior to SCH 58500 administration, Cycle 1/Day 1 (**a**, × 100), and at the end of the first cycle of SCH 58500 dosing, Cycle 1/Day 5(**b**, × 400). E: epithelial cells; S: stromal cells; T: tumor cells. SCH 58500 DNA was visualized using NBT/BCIP (dark blue color), and counter-stained with fast red (pink color).

variety of cell types. In cells collected from peritoneal aspirates, we found most of the positive rAd-p53 SCH 58500 signal in PMN cells with multilobed nuclear characteristics (Fig 5b). Taken together, the observation of high levels of p53 transgene expression (RNA) and upregulation of p21/WAF1 in peritoneal aspirates, we conclude that these cells were infected with rAd-p53 SCH 58500. Adenoviral vector-mediated gene transfer and expression in peritoneal cells via intraperitoneal injection was also evident in an ovarian cancer trial using an anti-erbB-2 single-chain antibody encoding adenovirus.[10]

In this study, we were able to demonstrate p53 transgene expression in both peritoneal aspirates and in tumor biopsy samples after multiple dose administration cycles of rAd-p53 SCH 58500. These data provide strong evidence that gene transfer was not abrogated by the presence of elevated levels of anti-adenovirus neutralizing factors. Furthermore, the increases in p21/WAF1, mdm-2, and bax gene expression suggest that the levels of rAd-p53 SCH 58500 delivered into tumors were sufficient to induce p53-mediated transcriptional activity in humans. It remains unclear whether the level of p53 expression achieved is sufficient for effective antitumor activity that would be evidenced by clinical responses. To this end, one of the trial participants, subject 52, had an interesting outcome. The bioanalytical analyses of her tumor biopsies showed both high p53 transgene expression and consistent and favorable p53 downstream gene responses.

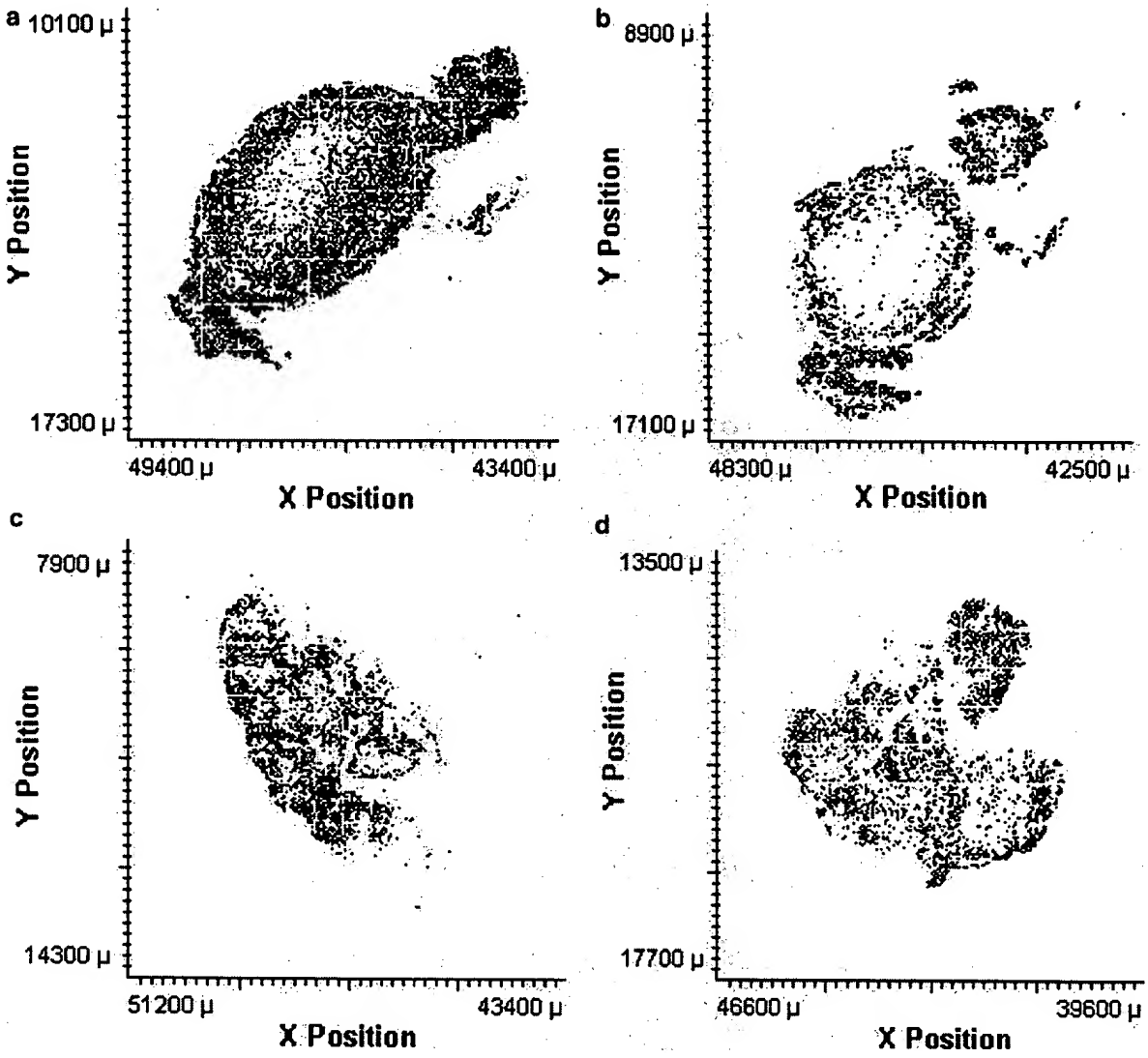

Figure 7 Laser scanning cytometry analysis of apoptosis (TUNEL). Four representative 5 μm tissue sections from subject 52 are shown. Tissues were scanned as described in the Materials and methods. Black dots represent TUNEL-negative nuclei; red dots represent TUNEL-positive nuclei. panels a and c show scans of tissue from Cycle 1/Day 1 and from Cycle 1/Day 5 post-treatment, respectively. TdT enzyme was included in the TUNEL reaction. The tissue sections were cut at different depths in the tumor biopsy. Panels b and d contain scans of tissue sections that were sequentially cut relative to the sections in panels a and c, respectively. In these panels, the TdT enzyme was omitted from the TUNEL reaction to detect nonspecific binding of the fluorescein-dUTP (panels b and d).

Subject 52's results reflected one of the best situations one might expect for a rAd-p53 gene therapy. We also observed that this subject had a positive clinical response to the rAd-53 SCH 58500 trial regimen. The results of her CT scan revealed that prior to treatment, subject 52 had malignant peritoneal fluid, an adrenal mass, a soft tissue mass at the ostomy site, and pulmonary nodules. The soft tissue ostomy site mass, pulmonary nodules, and malignant peritoneal fluid completely resolved by the end of Cycle 3. The size of the adrenal mass was reduced from $2.0 \times 2.5\,cm^2$ in size to $1.0 \times 2.0\,cm^2$ by the end of Cycle 3 (data not shown). Although this anecdotal response may not be attributable to rAd-p53 SCH 58500 regimen alone, subject 53 had previously failed three prior chemotherapy regimens. This suggests that rAd-p53 SCH 58500 was at least partially responsible for the response.

Acknowledgments

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A phase I/II trial of rAd/*p53* (SCH 58500) gene replacement in recurrent ovarian cancer

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Purpose: To determine the safety, gene transfer, host immune response, and pharmacokinetics of a replication-deficient adenovirus encoding human, recombinant, wild-type *p53* (SCH 58500) delivered into the peritoneal cavity (i.p.) alone and sequentially in combination with platinum-based chemotherapy, of patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer containing aberrant or mutant p53. **Methods:** SCH 58500 was administered i.p. to three groups of patients with heavily pretreated recurrent disease. Group 1 ($n=17$) received a single dose of SCH 58500 escalated from 7.5×10^{10} to 7.5×10^{12} particles. Group 2 ($n=9$) received two or three doses of SCH 58500 given alone for one cycle, and then with chemotherapy for two cycles. The SCH 58500 dose was further escalated to 2.5×10^{13} particles/dose in group 2. A third group ($n=15$) received a 5-day regimen of SCH 58500 given at 7.5×10^{13} particles/dose per day i.p. alone for cycle 1 and then with intravenous carboplatin/paclitaxel chemotherapy for cycles 2 and 3. **Results:** No dose-limiting toxicity resulted from the delivery of 236/287 (82.2%) planned doses of SCH 58500. Fever, hypotension abdominal complaints, nausea, and vomiting were the most common adverse events. Vector-specific transgene expression in tumor was documented by RT-PCR in cells from both ascitic fluid and tissue biopsies. Despite marked increases in serum adenoviral antibody titers, transgene expression was measurable in 17 of 20 samples obtained after two or three cycles of SCH 58500. Vector was detectable in peritoneal fluid by 24 hours and persisted for as long as 7 days whereas none was detected in urine or stool. There was poor correlation between CT scans and CA125 responses. CA125 responses, defined as a greater than 50% decrement in serum CA125 from baseline, were documented in 8 of 16 women who completed three cycles of the multidose regimen. **Conclusion:** CT scans are not a valid measure of response to i.p. SCH 58500 due to extensive adenoviral-induced inflammatory changes. Intraperitoneal SCH 58500 is safe, well tolerated, and combined with platinum-based chemotherapy can be associated with a significant reduction of serum CA125 in heavily pretreated patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer.

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It is projected that 23,400 women will be diagnosed with ovarian cancer and 13,900 will die from this disease during the year 2001.[1] These statistics make ovarian cancer the fifth leading cause of death among women in the United States. Ovarian cancer offers several unique opportunities for novel therapeutic intervention. First, despite the tendency to present at advanced International Federation of Gynecology and Obstetrics (FIGO) stage reflected by the observation that nearly 73% of ovarian cancers are no longer confined to the ovary at diagnosis,[2] this cancer often remains confined within the abdominal cavity throughout its course.[3,4] Second, initial, complete clinical responses are the expected norm following surgical cytoreduction and adjuvant systemic chemotherapy. Unfortunately, recurrence, progression, and death from disease is the eventual outcome for more than 75% of women diagnosed with epithelial ovarian cancer. Finally, because both primary[5,6] and secondary[7,8] surgical cytoreduction are cornerstones of the therapeutic approach to this cancer, tissue samples are often available for molecular genetic studies. Such studies have resulted in a better understanding of some of the molecular changes associated with ovarian cancer and how they may influence prognosis or response to treatment.

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Mutation of the *p53* tumor suppressor gene is one of the most frequent molecular genetic changes in cancer.[9,10] Wild-type p53 functions include roles in DNA repair following G1 cell cycle arrest, and directing irreparably damaged cells toward apoptotic pathways, thus maintaining the integrity of the genome.[11] Both *in vitro* and *in vivo* evidence suggests that cells with altered p53 function may be less responsive to certain chemotherapeutics than those that are able to express wild-type p53.[12,13] p53 dysfunction frequently results from mutations that can generate both missense and nonsense inactivating mutations. Rare gain of function mutations has also been described.[14] Nearly 70% of advanced stage ovarian cancers contain *p53* mutations and many of these mutations render the cancers p53 null.[15-17] Overall, *p53* null mutations can be associated with extremely poor prognosis reflected, at least in part, by early and distant metastasis.[4] These observations suggest that *p53* mutation is of fundamental importance in the progression of ovarian cancer.

Despite the association of distant metastasis with *p53* null mutation, most ovarian cancers usually remain confined to the abdominal cavity throughout their course and provide a unique opportunity for regional delivery of therapeutic agents. Intraperitoneal delivery of chemotherapy can provide a pharmacokinetic advantage over intravenous dosing by maximizing delivery of drug directly to tumor and minimizing systemic side effects.[18] A seminal study by the Gynecologic Oncology Group has demonstrated both response and survival advantage to women with minimal residual disease treated with intraperitoneal (i.p.) cisplatin after primary cytoreductive surgery for ovarian cancer.[19] Thus, ovarian cancer is a unique model for gene replacement strategies.[20,21]

Preclinical studies in several *in vivo* models have shown that delivery of wild-type *p53* to tumor cells can be achieved.[22-31] Extension of these studies, particularly in lung cancer, to phase I clinical trials has produced encouraging results.[32-36] To date, gene transfer in these systems has been accomplished with cationic lipids and a variety of viral vectors including the retroviruses and adenoviruses.[37] The use of an adenoviral vector, which has been rendered replication deficient, offers several advantages for therapeutic gene replacement strategies in cancer.[37] First, in contrast to retroviruses, adenoviral vectors efficiently transduce both dividing and quiescent cells. Second, they can be produced in high titers with particle numbers approaching the number of target cancer cells. Third, a bystander effect has been observed to occur following dosing with adenoviral vectors. Fourth, adenoviral vectors do not integrate into the host genome minimizing concerns regarding insertional mutagenesis. Taken together, these observations encouraged us to undertake a phase I/II trial of human recombinant adenoviral *p53* gene therapy with rAd/*p53* (SCH 58500) in recurrent ovarian cancer. Preliminary results have been presented in part.[38] The objectives of the study were: (a) to determine safety and tolerability to SCH 58500 alone and in combination with chemotherapy, (b) to determine the ability to transfer wild-type *p53* sequences into ovarian cancer cells *in vivo*, (c) to measure serum and ascites antibody responses to this form of therapy along with their influence on gene transfer, (d) to determine the pharmacokinetics of SCH 58500 in ascites and serum, and (e) to evaluate tumor response when multiple doses are delivered to patients over a 3-month period. Our findings indicate that gene transfer of SCH 58500 can be accomplished with minimal toxicity and that reduction in a surrogate marker, CA125, suggests the potential for clinical activity.

Methods

SCH 58500

SCH 58500 is a novel antineoplastic agent consisting of a recombinant adenoviral vector containing the cloned, human, wild-type *p53* tumor suppressor gene cDNA, which is under the control of the human cytomegalovirus immediate early promoter/enhancer element. SCH 58500 is derived from a type 5 adenovirus, a common serotype belonging to subgroup C, which has been rendered replication-defective through deletion of the viral genes E1a, E1b, and protein IX.[39] Vector is produced using GMP standards and has been tested for the presence of viral, bacterial, and other contaminants.

Tumor p53 *mutation status*

For screening, a representative primary or recurrent tumor sample from each patient who had signed informed consent was analyzed for *p53* mutation by immunohistochemistry utilizing both Pab 1801 (diluted 1:40) and Pab 240 (diluted 1:20) antibodies (Pharmingen, San Diego, CA). A positive stain with either antibody was considered to reflect aberrant tumor p53 protein and confirmed eligibility. Although this finding does not always reflect a p53 mutation, most authors consider immunopositive tumor to contain dysfunctional p53.[16] Sections with < 10% of cells showing nuclear staining were considered negative. Such individuals were excluded from study entry unless a *p53* DNA sequence abnormality could be documented.[16]

Antiadenovirus antibody assay

An ELISA was used to measure antiadenovirus antibodies specific for adenoviral coat proteins (antihexon antibodies) in serum and ascites. Samples were assayed in parallel with normal human serum and a ratio of sample titer versus normal human serum titer was calculated. If this ratio was less than 0.28 the sample was considered negative.

Patient eligibility and exclusion criteria

Only female patients at least 18 years of age previously treated with surgery and chemotherapy for ovarian, fallopian tube, or primary peritoneal carcinoma now presenting with pathologically confirmed recurrence of disease were eligible. An elevated CA125 was not required for entry. For those individuals without malignant ascites at recurrence, we required surgically documented i.p. disease accessible to laparoscopic or percutaneous biopsy. A tumor *p53* mutation was required as described above. All treated individuals functioned with a Karnofsky performance status of at least 60% and a minimum life expectancy of 3 months. Standardized clinical laboratory tests were within normal limits.

Previous whole abdominal radiotherapy was not allowed. Before the first treatment cycle a contrast study of the abdomen demonstrated free flow of instilled agent. Either a spiral CT with i.p. contrast, or i.p. Hypaque (Nycomed, Princeton, NJ) in 500 mL of normal saline followed in 30 minutes with a conventional flat plate x-ray was used to determine adequate peritoneal distribution of the infuseate. Three eligible, consented patients did not receive treatment with SCH 58500 based on poor distribution of contrast. Initially, only patients serologically positive for antiadenovirus type 5 antibody at screening were treated.

Patients not eligible for the study included those pregnant or nursing, and those with presence of serious bacterial, viral, fungal, or parasitic infection. Patients with evidence of adenoviral infection, as determined by ELISA, at screening were excluded and the chronic use of immunosuppressant therapy or use of another investigational drug within 3 months of proposed treatment with SCH 58500 also resulted in exclusion. Known human immunodeficiency virus (HIV)-positive individuals were also excluded. Short-term bolus use of dexamethasone as an antiemetic, or as premedication for paclitaxel, was allowed.

Registration

An institutional human subjects review board approved informed consent was obtained before the performance of any test or evaluation not considered standard of care for patients with peritoneal carcinomatosis. The same consent detailed the treatment with SCH 58500 and alternatives. No patient received SCH 58500 without signing an informed consent.

SCH 58500 delivery

SCH 58500 was infused over 20 minutes into the peritoneal cavity *via* a Hickman (Bard Systems, Salt Lake City, UT), Tenckhoff (CR Bard, Murray Hill, NJ), or Porta Cath (SIMS Deltec, St. Paul, MN) catheter. In preliminary studies, all catheters were shown to be compatible with SCH 58500. The goals of the infusions were to use a constant volume for each dose, with the volume large enough to generate adequate i.p. distribution, while at the same time providing a tolerable total volume. To achieve these goals, some variability of infusion volumes was required. Patients with clinically significant, preexisting ascites underwent drainage of the ascites before dosing with SCH 58500. Patients in group 1 then received SCH 58500 in 1000 mL of 0.9% NaCl. Group 2 and 3 patients received SCH 58500 in 250 mL, for 2 (Level 4), 3 (Level 5), and 5 (Level 6) days. By the end of five daily administrations (i.e., level 6), a total infusion volume of 1250 mL had been reached. Any additional ascites that accumulated during the course of administration of multiple doses was not removed except in one patient who had a large volume of ascites with her recurrent disease. Following this patient's first dose in cycle 1, the day 2 dose was delayed 24 hours to allow for ascites drainage. In the absence of ascites, each dose of SCH 58500 was infused in 500 mL of 0.9% NaCl so that by the end of five daily administrations (i.e., level 6), a total infusion volume of 2500 mL had been reached. Patients were then rotated every 15 minutes for 2 hours into Trendelenberg, right lateral, left lateral, and sitting positions.

Treatments

This sequential cohort, nonrandomized study, was conducted in three groups of patients. Table 1 outlines the treatment schema for i.p. SCH 58500. For group 1 patients, a single treatment dose of SCH 58500 was escalated from 7.5×10^{10} particles to 7.5×10^{12} particles per dose in four steps. Three patients were to be treated with SCH 58500 at each dose level in this group. The decision to escalate or expand a dose level was based on review of safety data for the patients within the single-dose level cohort under study or after day 7 of the first cycle when multiple cycles were given. A single, potential dose-limiting toxicity (DLT; see Results) prompted us to expand level 2 from three to six patients. After initial safety data were obtained, two additional antiadenoviral antibody negative individuals were allowed to enter at level 1. Therefore, a total of 17 patients were treated in group 1. Patients treated in this group were allowed to enter the multiple-dose group (see below) if they continued to meet all eligibility criteria.

For group 2 patients ($n=9$), cytotoxic chemotherapy was added in cycles 2 and 3 to allow differentiation between SCH 58500 side effects when it was given alone in cycle 1 and those related to its combination with chemotherapy. The dose of SCH 58500 was further escalated to 2.5×10^{13} particles although single-day dosing was increased first to 2 and then to 3 days per treatment cycle. Six group 2 patients received single-agent i.p. cisplatin at 100 mg/m^2 on day 1 of cycles 2 and 3 for dose levels 4 and 5 only. A 30-minute infusion of cisplatin was delivered in 1 liter of 0.9% NaCl 1 hour following the SCH 58500 infusion. The rest of the multiple-cycle patients were treated with intravenous chemotherapy. Paclitaxel at 175 mg/m^2 was infused over 3 hours immediately before SCH 58500 on day 1 whereas carboplatin was infused over 30 minutes immediately after SCH 58500 on day 3 of cycles 2 and 3 at dose levels 5 and 6. The carboplatin dose was based on an area under the curve

Table 1 SCH 58500 treatment regimens

Dose level	Particles delivered	Treatment days	Chemotherapy	Cycles*
Group 1 — single-dose SCH 58500				
1	7.5×10^{10}	1	None	1
2	7.5×10^{11}	1	None	1
3	2.5×10^{12}	1	None	1
4	7.5×10^{12}	1	None	1
Group 2 — escalating-dose SCH 58500 plus chemotherapy				
4	7.5×10^{12}	2	Cisplatin (i.p.)	3
5	2.5×10^{13}	3	Cisplatin (i.p.)	3
5	2.5×10^{13}	3	Carboplatin/Taxol (i.v.)	3
Group 3 — multiple-dose SCH 58500 plus conventional chemotherapy				
6	7.5×10^{13}	5	Carboplatin/Taxol (i.v.)	3

*Treatments were repeated at 28-day intervals.

(AUC) of 6 mg/mL min with the GFR based on the Cockroff-Gault formula for creatinine clearance.[40] With multiple-dose, multiple-cycle regimens, paclitaxel was before the vector because of *in vitro* evidence that this agent enhances transfection efficiency of SCH 58500.[23]

Once safety was confirmed by interpatient escalation, group 3 patients ($n=15$) were treated with intravenous carboplatin and paclitaxel in combination with SCH 58500 at 7.5×10^{13} particles, dose level 6. The number of doses of SCH 58500 was escalated from 3 to 5 per cycle. For patients in this group, either measurable or evaluable disease was required. Measurable disease was defined as a bidirectionally measurable lesion with clearly defined margins on physical exam or x-ray, computed tomography (CT), or magnetic resonance image analysis. Evaluable disease was defined as an elevated CA125 tumor antigen level greater than two times the institutional norm.

Tumor sampling. Twenty-four to 72 hours following single-dose SCH 58500, or 24 hours after the last dose of SCH 58500 in each multiple dose of the study agent, the peritoneal cavity was drained to obtain tumor cells. Patients who did not have ascites with recurrence of their cancer, or who had inadequate ascites following SCH 58500 dosing, were separately consented to laparoscopy for cycles 1 and 3 to obtain tumor and normal tissue samples for the various PCR studies. Pathologic, or cytologic, examination confirmed the presence of malignant cells in the samples of all patients.

Toxicity. The study design with escalating doses of SCH 58500 was aimed to determine dose-limiting toxicities utilizing standard WHO criteria. Any grade 4 (G1; WHO) toxicity, or a grade 3 (G3) toxicity lasting greater than 1 week, was to be considered dose limiting (DLT), unless the event was obviously related to another procedure (e.g., anemia due to chronic test phlebotomy).

Nausea, vomiting, and anorexia were excluded as dose-limiting toxicities in patients receiving chemotherapy.

Patient monitoring. All single-dose patients were treated as inpatients. A qualitative ELISA kit (Cambridge Biotech, Worcester, MA) was used to confirm the absence of viral shedding in urine and stool samples before dosing, during treatment, and before hospital discharge. Vital signs were obtained before and periodically following the administration of SCH 58500. Physical exams, performance status, weight, and adverse event assessments were performed daily whereas the patients were hospitalized and at prescribed intervals following discharge: Day 7, 14, 21, and 2 months after dosing, then every 3 months until death. Laboratory data included serum and ascites sampling for pharmacokinetic studies, complete blood counts (CBC), fibrinogen, fibrin split products, PT, PTT, serum C_3, C_4, CH_{50}, electrolytes including magnesium, blood glucose, and CA125. Laboratory tests were performed at each visit, except CA125, which was monthly. Baseline abdominal and pelvic computed tomograms were obtained along with a chest x-ray before dosing. Follow-up scans were obtained at 28 days and as clinically indicated for patients who received multiple cycles of SCH 58500. Lesions were measured in two perpendicular directions. Standard response definitions were used, i.e., complete response (CR) required the disappearance of all gross evidence of disease for at least 4 weeks; partial response (PR) required a reduction in lesion size in excess of 50% lasting at least 4 weeks; progressive disease was said to have occurred on the basis of a 25% increase in lesion size; all other measurable disease cases were considered to define stable disease (SD). As an additional measure of response, changes in serum CA125 were evaluated. The 50% and 75% CA125 responses as defined by Rustin et al[41,42] have been shown to correlate well with conventional CT response measures.

Documentation of gene transfer and viral persistence. Total RNA was extracted and cDNA prepared from ascites or tissue biopsies. The QIAamp 96 Spin Blood Kit (Qiagen, Valencia, CA) was used to extract viral DNA from serum. Polymerase chain reactions were carried out utilizing primers specific for both the adenovirus and the *p53* gene as well as β-actin or glyceraldehyde 3-phosphate dehydrogenase (G3PD) collectively referred to as housekeeping genes or HKG. The MIMIC® (Clontech, Palo Alto, CA) reverse transcriptase technique allowed for semiquantitative comparisons of mRNA levels. Tripartite leader sequence-specific primers permitted the resolution of SCH 58500 sequence from host p53 sequence (See Results).

In situ *PCR.* Five-micrometer sections of formalin-fixed, paraffin-embedded tissue were placed on 1.2-mm silane-coated Perkin-Elmer (Foster City, CA) *in situ* PCR glass slides. Slides were baked 2–3 hours at 60°C to reduce RNA content. Slides were then treated sequentially with 0.02 N HCl, Proteinase K, and acetic acid. Thirty-five PCR cycles were carried out using dinitrophenyl-labeled primers (DNP) specific for SCH 58500. Following incubation with anti-DNP antibody conjugated to alkaline phosphatase, visualization was achieved by adding nitro-blue tetrazolium-5-bromo-4-chloro-3-indolyl phosphate as substrate and counterstaining with Nuclear Fast Red. Negative staining was pink, whereas positive staining was blue and nuclear.

Statistics. Differences in toxicities between SCH 58500 and SCH 58500 plus chemotherapy cycles were evaluated with Fisher's Exact test, 2-tailed. Mean CA125 changes were analyzed by ANOVA, or *t* tests as appropriate. A P value of $<.05$ was required for significance.

Results

Patient selection and characteristics

One hundred and fifty-five patients signed informed consent and entered into screening at three sites. Overexpression of p53 protein by immunohistochemistry was demonstrated for 79 of the 155 (51%) cancers tested. The Iowa site carried out p53 gene sequencing on 25 of 28 p53 immunonegative cancers screened at that institution. An additional 8 patients (7 with *p53* null mutations) met the p53 eligibility criteria in this fashion. So that 57% (88/155) of patients screened were eligible for entry. Overall, 36 patients were dosed with SCH 58500. Five patients were treated on both the single-dose arm of the study and the later multiple-dose program. Therefore, 41% (36/88) of the eligible patients representing

23% (36/155) of the patients screened were actually treated with SCH 58500. The mean age of the individuals dosed was 60 years (range: 39–76). Demographic and disease-related parameters for this cohort of heavily pretreated individuals with recurrent peritoneal carcinomatosis are summarized in Table 2. Most individuals had recurrent ovarian cancer. The mean interval from primary diagnosis to dosing with SCH 58500 was 778 days (range: 115–2360 days). The mean platinum-free interval to dosing with SCH 58500 was 263 days (range: 37–711 days). Nine of 36 patients had a platinum-free interval of more than one year. The mean number of prior chemotherapy regimens was 2.8 with 22% of individuals receiving four or more prior regimens and 33% receiving just one prior regimen. All individuals had previously received platinum-based chemotherapy, and all but two had prior treatment with a taxane. Three patients had recurrent disease evaluable only on the basis of laparoscopic biopsy. Fourteen patients could be considered to have small-volume disease, arbitrarily defined as less than or equal to 2 cm.

Toxicity

Two hundred and thirty-six different signs or symptoms were recorded as adverse events. These varied from single patient WHO grade 1 (G1) events such as increased earwax and nonspecific breast complaints to a G4 transient ischemic attack. Because adenoviral particles delivered in this study are more than a log higher than in any previously reported gene therapy trial, great attention was paid to complete reporting of all potential adverse events. From a practical standpoint, we have chosen to present all serious G3 or G4 events, but only the G1 and grade 2 (G2) events that occurred in three or more treated individuals. This of course underreports the total number of minor adverse events. Each treatment-related adverse event is recorded as the highest-grade toxicity experienced out of all treatment cycles received by that patient as explained in the legend to Table 3. The events are listed in this table on the basis of occurrence in either the single-dose or multiple-dose groups. To show that there was no cumulative toxicity, we have listed the five patients who were treated with multiple-dose SCH 58500 after completion of the single-dose portion of the study separately. The most common adverse events in the single-dose group included fever (47%), nausea (41%), edema (41%), abdominal complaints (41%), and anemia (29%). Seven patients experienced ≥5 different adverse events whereas only 1 patient had no adverse events at all. Eight G3 or G4 adverse events were reported in four patients. These included anemia (2:G3; 1:G4), abdominal complaints (1:G3), dehydration (1:G3), pain (1:G3), tachycardia (1:G3), and vomiting (1:G3). There was no unusual toxicity in the two serum antiadenoviral antibody negative patients dosed at level 1.

Fever was also the most common adverse event experienced by 100% of the multiple-dose patients. This sign developed within 2 to 4 hours of dosing. The highest reported temperature was 40.5°C. Four cycles were accompanied by G3 febrile responses (>40°C) among two different patients. After fever was noted in the initial dosing cohorts, patients were generally given prophylactic acetaminophen. The subsequent febrile responses were attenuated, but this may also have been due to the steroid premedication given before chemotherapy for cycles 2 and 3. Figure 1 demonstrates this observation graphically for a patient treated at dose level 5. In the multidose cohort, the next most frequent signs and symptoms related to SCH 58500 included hypotension (89%), a variety of abdominal complaints (79%), hypertension (68%), nausea (63%), tachycardia (58%), vomiting (58%), and fatigue (53%) — often in the same patient and cycle as the hypertension was noted. The blood pressure changes prevalent in this group were not seen at all in the single-dose group, but they were generally considered mild because only one G3 toxicity occurred. All of these most common adverse events, except hypertension, also occurred in 100% of the single-dose patients who reenrolled in the multiple-dose regimen. However, there was no progression of toxicity grade in those re-treated relative to those initially treated at the same dose of SCH 58500.

Forty-seven G3 or G4 toxicities were reported in 13 patients who received multiple-dose SCH 58500. Many of the new WHO G3 toxicities were probably related to chemotherapy because they usually appeared in cycles 2 and 3. The patient with congestive heart failure also developed a G4 neutropenia with concomitant thrombocytopenia in cycle 3. A few new low-grade adverse events were reported when chemotherapy was combined with SCH

Table 2 Study cohort demographics

Primary diagnosis	
Ovarian cancer	30
Peritoneal cancer	5
Fallopian tube cancer	1
Prior chemotherapy	
Mean number of regimens	2.8 range [1–8]
Mean treatment cycle	13 range [5–31]
Mean drugs × cycles	24.4 range [8–78]
SCH 58500 treatment	
Single dose	17
Multiple dose	24
Both	5
Interval: (days)	
Diagnosis to SCH 58500	777.7 range [115–2360] median=630
Platinum-free to SCH 58500 first dose*	263 range [37–711] median=261
Disease status	
Elevated CA125	33
CT measurable lesions†	
>2 cm	22
≤2 cm	5
Normal CA125 and CT scan	3

*The platinum-free interval for nine patients was ≥365 days.
†All CT-measurable disease was accompanied by an elevated CA125.

Table 3 Treatment-related adverse events*

Adverse event	Single-dose SCH 58500 (*N=17*)				Multiple-dose SCH 58500 (*N=19*)				Single- and multiple-dose SCH 58500 (*N=5*)			
	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
Abdominal complaints†	4	2	1	0	4	4	7	0	2	1	2	0
Anxiety	0	0	0	0	2	0	0	0	2	0	0	0
Anemia	1	1	2	1	0	3	1	0	0	0	1	1
Anorexia	1	0	0	0	5	0	1	0	2	0	0	0
Asthenia	0	0	0	0	2	4	2	0	2	0	0	0
Bradycardia	0	0	0	0	0	0	1	0	0	0	0	0
Chills	1	0	0	0	7	3	0	0	0	0	0	0
Cellulitis (Port)	1	0	0	0	3	1	0	0	0	1	0	0
CHF	0	0	0	0	0	0	1	0	0	0	0	0
Dehydration	0	0	1	0	2	0	0	0	0	0	1	0
Diaphoresis	2	0	0	0	2	0	0	0	0	0	0	0
Diarrhea	0	1	0	0	7	0	1	0	1	0	1	0
Dizziness	1	0	0	0	3	2	0	0	2	0	0	0
Dyspnea	1	0	0	0	3	1	0	0	0	0	0	0
Edema	6	1	0	0	0	1	1	0	1	0	0	0
Fatigue	2	2	0	0	3	3	4	0	2	3	0	0
Fever	3	5	0	0	1	16	2	0	2	3	0	0
Gastritis	0	0	0	0	0	0	1	0	0	0	0	0
Headache	0	0	0	0	8	1	0	0	1	0	0	0
Hypertension‡	0	0	0	0	10	3	0	0	1	1	0	0
Hypotension§	0	0	0	0	11	3	2	0	4	1	0	0
Lethargy	0	0	0	0	0	1	1	0	0	0	0	0
Loss of Consciousness	0	0	0	0	0	0	1	0	0	0	0	0
Malaise	1	0	0	0	3	4	2	0	2	0	0	0
Nausea	7	0	0	0	2	3	7	0	1	1	3	0
Neutropenia	0	0	0	0	0	0	0	1	0	0	0	0
Pain¶	1	2	1	0	4	2	1	0	0	2	0	0
Peritonitis	0	0	0	0	0	0	2	0	0	0	0	0
Tachycardia	1	0	1	0	11	0	0	0	5	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	1	0	0	0	0
TIA	0	0	0	0	0	0	0	1	0	0	0	0
Vomiting	4	1	1	0	2	3	6	0	2	2	1	0

*All WHO G3 or G4 toxicities and any toxicity, including G1 and G2 reported by three or more patients. Values are number of patients with a given event in each group. Only the worst toxicity level is reported for each patient, i.e., a G2 fever in cycle 1, G1 in cycle 2, and G3 in cycle 3 appears as a single entry, G3.

†Includes abdominal enlargement, bloating, contractions, cramping discomfort, distention, fullness, pain, pressure, or tenderness.

‡Hypertension: G1 = asymptomatic transient increase by greater than 20 mmHg or to >150/100 if previously within normal limits; no treatment required. G2 = recurrent or persistent increase by greater than 20 mmHg or to >150/100 if previously within normal limits; no treatment required. G3 = requires therapy. G4 = hypertensive crisis.

§Hypotension: G1 = ≥20 mmHg decrease in SBP or DBP requiring no therapy (including transient orthostatic hypotension). G2 = ≥20 mmHg decrease in SBP or DBP requiring fluid replacement or other therapy but not hospitalization. G3 = requires therapy and hospitalization. G4 = life-threatening.

¶Includes pain, back pain, breast pain, chest pain, substernal chest pain, or flank pain.

58500. These included lower extremity myalgias, myoclonus, ileus, gastritis with hematemesis, hyperactive bowel sounds, pulmonary hypertension, peripheral neuropathy, oliguria, mucositis, port site cellulitis, agitation, generalized weakness, and cachexia. Only three multiple-dose patients had ≤3 adverse events whereas 11 reported ≥10 adverse events. Overall, G3 toxicities accompanied approximately one-third of the treatment cycles. Antiemetics generally alleviated the gastrointestinal symptoms and were used prophylactically at the investigator's discretion. As the total amount of SCH 58500 delivered was increased, there was a trend toward more G3 adverse events: the number of adverse events went from 0.5 to 1.6 to 2.9 per patient as the treatment was advanced from single dose to level 4/5 and then to level 6. The addition of chemotherapy produced additional nausea and vomiting (P=.03, Fisher's exact test, 2-tailed). There was no trend for adverse events to worsen in a given individual as the number of doses delivered was increased. Likewise, there was no evidence of cumulative toxicity as patients progressed from the single-dose arm to treatment with multiple doses and multiple cycles.

One G4 toxicity occurred in a patient who became anemic in cycle 2. This complication along with the other G3 toxicities due to anemia occurred in individuals who were anemic at the start of the study and has been attributed to the volume of blood drawn for the multiple laboratory studies,

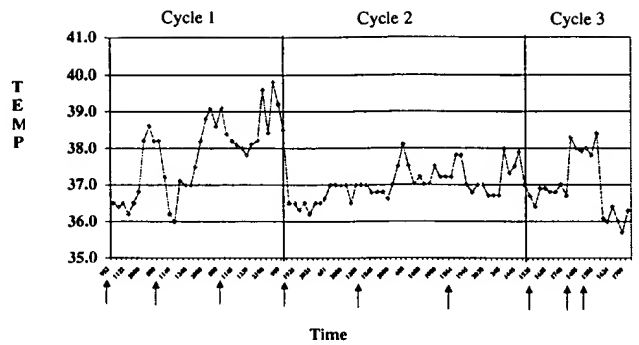

Figure 1 Typical febrile response to SCH 58500 over time with multiple doses and cycles. ↑ indicates dose of i.p. SCH 58500 delivered. SCH 58500 toxicity by treatment cycle.

anemia of chronic disease, and anemia secondary to chemotherapy treatments. There was no evidence of hemolysis in any patients. One individual with liver metastasis and progressive disease following single-dose SCH 58500 at level 2 developed a potential DLT reflected by an increase in alkaline phosphatase from 57 U/L at baseline to 742 U/L 28 days following dosing. This was accompanied by an increase in AST to 106 U/L and ALT to 111 U/L. She refused a follow-up CT scan and died 51 days after dosing. The family declined a request for an autopsy. Because of this adverse event, three additional patients were treated at this dose level before moving on to level 3. Therefore, although one cannot rule out SCH 58500 as a cause of this potential DLT, the investigator felt that the clinical course of this patient was quite consistent with progression of disease as the proximal cause of these events. Supporting this conclusion was the additional observation that no other patient, at any dose, developed evidence of G3 or G4 hepatic toxicity. Five individuals (14%) developed potentially worrisome small bowel obstructions between 2 and 8 months after initial dosing. These events occurred both on the single-dose (n=2) and multiple-dose (n=3) arms. Only one episode was attributed to SCH 58500, rather than to disease progression and/or underlying adhesions. All five resolved with conservative nonsurgical management. Two i.p. catheter-related infections also complicated treatment and led to patient removal before completion of the anticipated number of cycles. Both were associated with abdominal Hickman (Bard Systems, Salt Lake City, UT) catheters. One of these individuals developed vancomycin-resistant enterococcal peritonitis. She was found to be a nasal carrier of this organism. Another individual developed a sterile pelvic abscess. Both patients received only five doses of SCH 58500 alone before withdrawal from the multiple-dose arm. Overall, 82.2% of the planned doses of SCH 58500 were delivered. In addition to the catheter problems outlined above, failure to complete the planned number of cycles of chemotherapy plus SCH 58500 resulted from disease progression (two patients), side effects (one patient), and a withdrawn consent (two patients).

Pharmacokinetics. SCH 58500–specific PCR was carried out on serum samples of all patients during cycle 1. Samples were obtained pretreatment at 15, 30 minutes, 1, 2, 4, 6, 12, 24, 36, 48, and 72 hours; and days 7, 14, 21, and 28 following administration of SCH 58500. Detectable serum levels of SCH 58500 were found in seven patients. In four of these, the levels were detectable but not quantifiable. Only one patient had a quantifiable level after 24 hours. There was no vector shedding in either urine or stool of any patient as determined by ELISA assay. One patient underwent a therapeutic thoracentesis 72 hours after dosing with SCH 58500 on the single-dose arm. The pleural fluid was positive for vector by ELISA. Patient peritoneal fluid analysis consistently demonstrated the presence of viral DNA for 24 hours. For a subset of three patients, viral DNA was detected on day 6 for one patient and day 7 for two. ELISA positive peritoneal fluid was noted for periods in excess of 1 year following the last dose of SCH 58500. However, we were unable to culture live virus or demonstrate infectivity by the FACS assay[43] from the prolonged ELISA positive fluid.

Tumor sampling

Following cycle 1, 22 patients had ascites sampled, 5 had a laparoscopic biopsy, and 11 had both. Only ascitic fluid was sampled after cycle 2. Following cycle 3, 8 patients had ascitic fluid sampled, 5 underwent laparoscopic biopsy, and 1 had both procedures.

Determination of gene transfer

The unique tripartite leader sequence incorporated into the recombinant *p53* gene sequence allowed us to differentiate

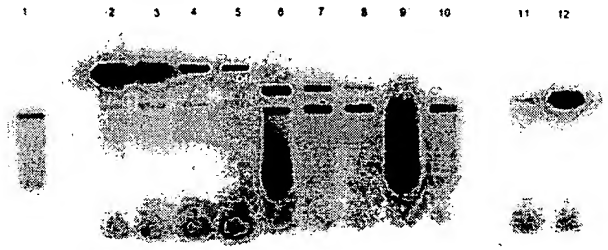

Figure 2 MIMIC® PCR assessment of gene transfer. The numbers correspond to lane numbers in a 3% agarose gel. Total RNA was extracted from a tumor biopsy obtained laparoscopically from a patient 72 hours after administration of a single dose of 2.5×10^{12} particles of SCH 58500. For this sample, the effect of serial dilution of β-actin message template cDNA prepared from tissue RNA and added to a MIMIC® PCR reaction is reflected by the decreasing intensity of the upper band in lanes 2–5 of the agarose gel. A precisely calculated amount (500 molecules) of β-actin MIMIC® has been spiked into the PCR reaction and results in the generation of the lower band in the same lanes. Lanes 11 (500 molecules of β-actin MIMIC®) and 12 (100,000 molecules of β-actin MIMIC®) have been used for quantitative calculations. Similarly 500 molecules of the p53 MIMIC® have been spiked into the PCR reactions run in lanes 6–8 from serial dilutions of the template cDNA. In these lanes the MIMIC® product is the lower band and corresponds to the single band in lane 1 (500 molecules of p53 MIMIC® without template cDNA). The upper band in lanes 6–8 represents p53 product containing the tripartite leader. In the absence of transfection, as in lanes 9 and 10, no upper band is seen because the wild-type p53 sequence does not contain sequence that will bind the leader sequence specific primers.

mRNA expression due to transduced *p53* gene from any host wild-type p53 mRNA co-isolated from contaminating normal cells. Figure 2 shows a gel containing both sample and MIMIC® PCR reaction that demonstrates this principle. The equivalence of band intensities in lane 7 at a 1:4 dilution of template cDNA allows for the calculation of the number of molecules of p53 mRNA isolated from the sample normalized for the sample β-actin message content. In this case 1.6 molecules of p53 transgene mRNA per 1000 molecules of β-actin message were detected. Similar studies were carried out using mRNA isolated from cells separated from ascites or from biopsies obtained at the indicated times and cycles for all patients treated. Figure 3 summarizes these results. Transgene expression was seen at doses as low as 7.5×10^{10} particles and consistently at or above 7.5×10^{11} particles per dose. Three samples were negative for β-actin and were excluded from this analysis. In two cases samples thawed during shipment. In another patient, a tumor biopsy obtained at day 3 was negative; however, her ascites was positive at day 7. Overall, transgene expression at the RNA level occurred in 3 of 5, 4 of 4, 3 of 3, 8 of 11, 9 of 11, and 25 of 28 samples analyzed for SCH 58500 doses of 7.5×10^{10}, 7.5×10^{11}, 2.5×10^{12}, 7.5×10^{12}, 2.5×10^{13}, and 7.5×10^{13} particles per dose, respectively. The most significant observation from this analysis is that transgene expression was detectable in 17 of 20 (85%) samples following multiple dosing with SCH 58500.

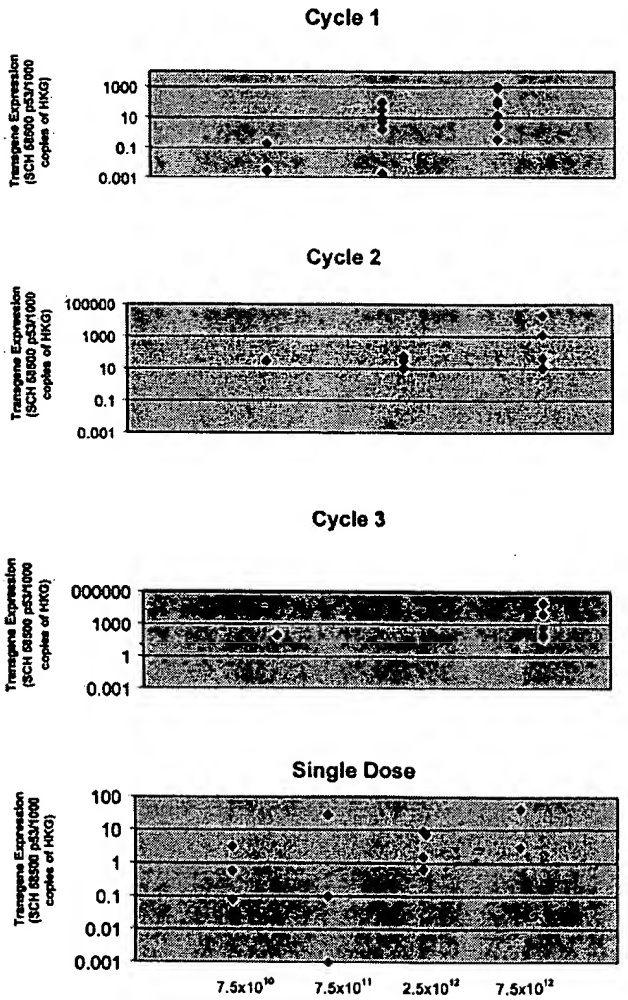

Figure 3 *p53* gene transfer following multidose i.p. delivery of SCH 58500. MIMIC® PCR reactions were carried out as described in the legend to Figure 1. Measurable levels of mRNA are plotted in the graphs according to cycle and dose of SCH 58500. Seven additional samples were RT-PCR positive, but at expression below levels that could be quantitated. Only 9 of 62 samples expressing β-actin were n gative for p53 transgene expression.

Demonstration of vector-encoded DNA in tumor target cells

The RT-PCR transgene expression data presented above were generated from ascitic fluid cell pellets or tissue biopsies. Such samples may contain normal cells as well as tumor cells. Thus, whereas we have clearly demonstrated transgene expression in our biopsy and ascitic fluid samples, we have not demonstrated the presence of either agent or transgene product from within tumor cells. To achieve this goal, *in situ* PCR was carried out on sequential tissue samples from a single patient. The primers used were specific for SCH 58500. Figure 4A shows a sample obtained before dosing with SCH 58500. The pink stain indicates the absence of viral DNA. This contrasts with the blue nuclear stain of the sample shown in Figure 4B obtained after three cycles of SCH 58500. A negative control is shown in Figure 4C wherein *Taq* polymerase was omitted from the reaction. These results clearly demonstrate the presence of viral DNA within tumor cells. Finally, Figure 4D shows a hematoxylin and eosin stained section corresponding to the tissue sample in panels B and C. In this figure, apoptotic bodies and dying tumor cells are readily differentiated from healthy tumor cells deeper within the biopsy.

Antiadenoviral antibody response

Baseline serum antiadenoviral antibody titers ranged from 1:160 to 1:16,000 before the first dose of SCH 58500. A 2-fold rise in titer could be seen by day 3 following i.p. SCH 58500. Increases in titer on day 28 ranged from 2- to 1600-fold over screening values. For patients enrolled in the multiple-dose regimens, or those re-treated with SCH 58500, a transient decrease in antibody titer on the order of 2- to 4-fold was sometimes seen. Twelve- to fifty-fold increases over the baseline titer were observed for up to 11 months following a single dose of SCH 58500. With multiple dosing, continued increases in titer were measured to as high as 1:2,560,000. An immune response was documented in one of the two individuals treated at level 1 who entered with negative titers. There was no apparent correlation between change in antibody titer and alterations in CA125 levels (see below). Likewise, there was no correlation between the dose of SCH 58500 and the mean change in antibody titer or the mean change in antibody titer with transgene expression (data not shown).

Measures of response

Table 4 compares conventional CT response determinations to the change in CA125 measured from study entry to study

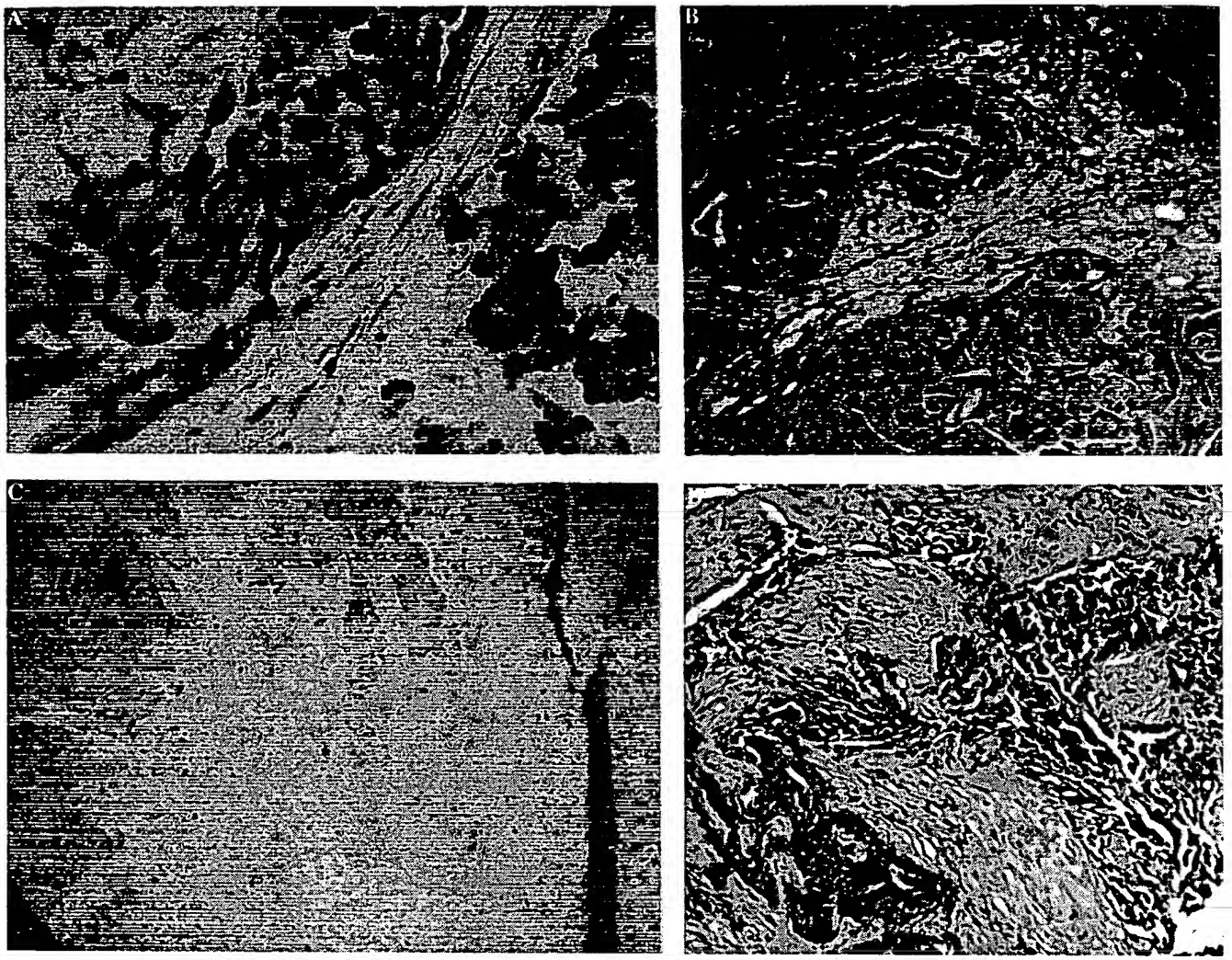

Figure 4 Analysis of tumor biopsies after i.p. SCH 58500. *In situ* PCR measurement of viral DNA. **Panel A:** Biopsy from a patient before SCH 58500 (×400). **Panel B:** Biopsy from a patient after three cycles of SCH 58500 (×200). **Panel C:** 5-μm section from the same sample as **(4-B)** but a negative control based on omission of Taq polymerase from the PCR reaction (×40). **Panel D:** An H and E section from the same sample (×200).

exit. Three tumors, all in group 1, were CA125 negative (<35 U/dL) at the time of enrollment. Although all three had biopsy-proven recurrence of disease, none had CT-measurable disease either. Six other individuals with elevated CA125 levels did not have CT-measurable disease at study entry. Two individuals without CT-measurable disease were treated in both group 1 and group 2. There were no CR or PRs documented by CT scan. On the contrary, the best CT responses were four cases of SD, three from group 1 and one from group 2. The most striking feature of the follow up CT scans was the frequency that disease progression was called on the basis of the development of new lesions — documented in 18 treatment regimens. For nine of these cases, apparent disease progression was accompanied by at least a 26% decrease in CA125 from baseline. In several of these cases, apparent CT progression was found at laparoscopy to represent a pocket of inflammatory cells. Five of nine patients treated in groups 2 and 3 with purported CT disease progression demonstrated at least a 50% CA125 response. In contrast, for six of nine group 1 patients, the development of new CT lesions was accompanied by at least a 25% increase in CA125 disease. Together these observations are consistent with the hypothesis that the new CT lesions often occurred due to SCH 58500–induced inflammatory changes rather than disease progression. This conclusion prompted us to carry out a more detailed analysis of the response to SCH 58500 on the basis of the associated CA125 change from baseline.

Serum CA125 levels were measured immediately before dosing with SCH 58500 and following each treatment cycle. Two of the three patients with baseline CA125s <35 U/dL more than doubled their CA125 during study. CA125 could thus be considered a valid response parameter for all but a single patient. In addition, it is clear that the inflammatory response initiated by SCH 58500 did not uniformly give rise to an increase in CA125 by itself. The percent change in CA125 was then calculated for each individual for each treatment cycle, and overall at 28 days after study

Table 4 Relationship of CT-based response to CA125 response

Treatment regimen	Best response	Cases	CA125 change			
			>+25%	+24% to −25%	−26% to −74%	>−75%
Single-dose SCH 58500	SD	3	–	1	2	–
	PD	3	3	–	–	–
	PD^n	9	6	1	1	1
	NM	2	1	1	–	–
Multiple-dose SCH 58500	SD	1	–	1	–	–
	PD	9	3	4	1	1
	PD^n	9	2	–	3	4
	NM	5	2	1	–	2

SD=stable disease; PD=progressive disease by enlargement of response lesion; PD^n=progressive disease by virtue of new lesions; NM=no measurable disease.

completion. Comparison of CA125 levels following treatment with SCH 58500 alone at $\leq 2.5\times10^{11}$ particles/dose to treatment at $\geq 2.5\times10^{12}$ particles/dose demonstrated a mean increase in serum CA125 of 94% versus a mean decrease of 8.5% at the higher dose (P=.07, 2-tailed, unequal variances). Thus, SCH 58500 alone at higher doses provides a favorable change in CA125 not seen at lower doses of vector. Figure 5 summarizes the CA125 response data. Dosing with SCH 58500 alone resulted in a mean decrease in CA125 of 33.6% for the 16 of 41 women whose CA125 levels declined during the 28 days following dosing. These declines ranged from 4% to 77%. One additional patient's CA125 was unchanged at 46 U/mL. In contrast, with the addition of chemotherapy for cycle 2, 15 of 18 women demonstrated a mean decrement of 47.7% in their pre-cycle 2 CA125 levels. This result indicates enhanced CA125 response over treatment with SCH 58500 alone. For cycle 3, 11 of 16 of treated women showed a mean decline in CA125 levels of 36.6% compared to cycle 2 day 28 CA125. Thus, a continued response was seen in excess of that seen with SCH 58500 alone. Overall, 2 of 14 women demonstrated a 50% or greater decline in CA125 following a single dose of SCH 58500. For the 16 women who completed all three multiple-dose cycles, 8 registered a CA125 decline ≥54% from study entry. Among all responders, the average decline in CA125 was 60.1% (P=.06 vs SCH 58500 alone). Favorable changes in CA125 levels were independent of the time interval from initial diagnosis to SCH 58500 dosing. Likewise, the number of prior treatment cycles and regimens did not preclude a CA125 response and there was no apparent relationship between transgene expression and CA125 response.

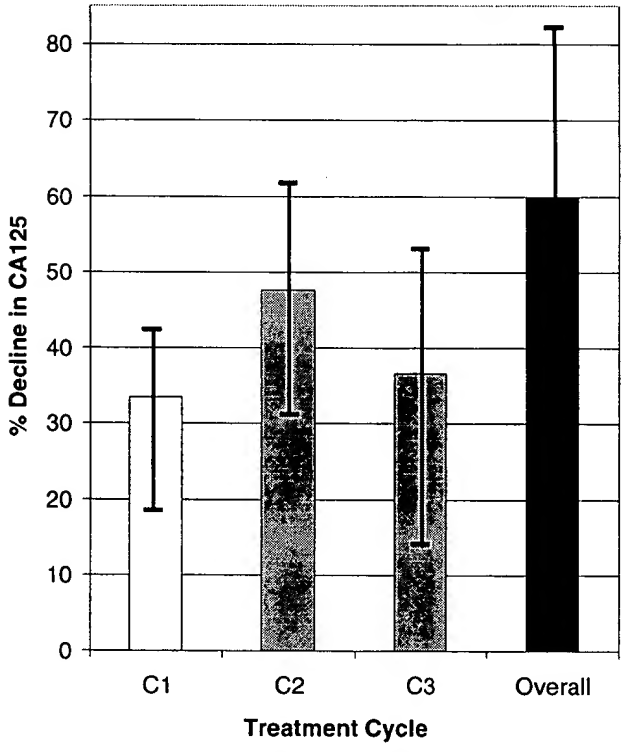

Figure 5 CA125 responses following treatment with SCH 58500. In cycle 1 (C1: □) all patients received SCH 58500 alone. Cycles 2 and 3 (C2, C3: ■) includes all patients who received chemotherapy in addition to SCH 58500. The mean decline in serum CA125 was calculated for responders only. Overall (▨) is the average percent decline at the end of the study for individuals who responded relative to their screening CA125 level. In each case, CA125 is measured over a 28-day interval or at the beginning of the subsequent treatment cycle. The error bars are 95% confidence limits of the mean.

Discussion

Because p53 tumor suppressor gene dysfunction is seen in 50–60% of all human malignancies,[9,10] this gene has become a leading candidate for clinical studies involving gene transfer technology for the treatment of cancer. Preclinical studies utilizing a variety of cell lines have shown efficient transduction, cell cycle arrest, apoptosis, and enhanced cell death following treatment with adenoviral constructs containing wild-type *p53* gene sequence alone and in combination with cytotoxic chemotherapy.[22-31] Although some evidence suggests that this effect may not be solely dependent on the presence of mutant p53, others have found greater efficacy when the endogenous p53 is mutant.[31,44] Results from *in vitro* xenograft models of several malignancies, including ovarian cancer, suggest

promise for the strategy of *p53* gene replacement as a novel cancer therapeutic approach.[25,30,31,45] There is no apparent effect of wild-type p53 overexpression on normal tissue such as fibroblasts.[46] Of particular relevance is the preclinical observation that the effects of *p53* gene replacement are synergistic with both cisplatin and paclitaxel, the two mainstays of ovarian cancer chemotherapy.[22,23,30] Most clinical data to date with *p53* gene replacement are limited to intratumoral injections,[32-36] in contrast to the body cavity exposure of the large surface area of the peritoneal cavity exposed to SCH 58500 in the present study. Finally, although carcinogenesis clearly involves multiple gene defects, data support a therapeutic approach that corrects only a single, critical gene defect.[47,48]

Intraperitoneal therapy of ovarian cancer was initially reported in 1955 by Weisberger et al.[49] In the past 5–10 years encouraging results from the i.p. delivery of a variety of chemotherapeutics and biologics have been reported both for primary therapy and for small-volume recurrent or persistent disease.[19,50-55] These studies have suggested the importance of treating small-volume disease and have established safety and symptom data to which one can then compare results of i.p. gene therapy. Indeed, encouraged by these data, phase I trials of the herpes simplex thymidine kinase/ganciclovir system,[56-58] and adenoviral E1a gene therapy,[59] have been initiated for recurrent ovarian cancer. Early results of phase I/II retroviral and adenoviral *BRCA1* i.p. gene replacement have also been published.[60,61]

Several potential limiting factors associated with i.p. drug delivery of gene therapy *per se* have been identified. For example, the uniformity of drug distribution is always of concern. For the present study, all patients were required to have widespread i.p. distribution verified by a pretreatment radiologic study before initial dosing. The fraction of the cancer cells that needs to be transduced in order for a clinical effect to be measured is unknown. It is clear that not all tumor target cells will be transduced, especially with a single administration of vector because the depth of penetration into tumor appears limited.[62] Furthermore, there is concern that the accumulation of adhesions and the host immune response may prevent effective gene transfer with repetitive dosing of a viral vector. In the present study, multiple laparoscopies on the same patient provided the opportunity to demonstrate that individual inflammatory response was highly variable and that peritoneal distribution can clearly change over time.

The present study was designed to determine the safety of the SCH 58500 adenoviral vector delivered into the peritoneal cavity of women with refractory ovarian cancer. No maximum tolerated dose (MTD) was established as the protocol-defined DLT was not met. The doses delivered ranged from 7.5×10^{10} to 7.5×10^{13} particles per i.p. infusion. The highest dose tested was limited by practical considerations including the i.p. delivery volume for multiple-day dosing regimens. Tolerance to SCH 58500 was excellent with manageable toxicity. Aside from fever, the toxicity profile, even with multiple cycles was similar to that reported for i.p. chemotherapy in general.[19,50,51] Overall, 82.2% of the planned doses were delivered and this included 219 of 270 (81%) doses on the multiple-dose/multiple-cycle regimens. By way of comparison, 84% of the planned i.p. chemotherapy was delivered in a similarly sized study by Morgan et al[51] whereas 76.8% of the planned i.p. cisplatin doses were delivered in the large cooperative group study reported by Alberts et al.[19] Progression of disease was the most common reason for incomplete dosing rather than side effects in the present study.

Vector-specific gene transfer and mRNA expression of SCH 58500 was seen at doses as low as 7.5×10^{10} particles/single dose and was frequently detected in patients that received 7.5×10^{11} particles/dose. It seemed desirable to increase the dose level and number of doses to a maximum based on the theoretical tumor burden within the peritoneal cavity and the need to maximize exposure of tumor cells to SCH 58500. Preclinical modeling indicated that multiple fractionated doses of SCH 58500 had greater efficacy than a single bolus injection.[22]

Early concerns that the presence of serum neutralizing antibodies to the adenovirus might limit its effectiveness, particularly with repetitive exposure are not borne out by our results.[63] Preclinical work with immunized rodents treated with intratumoral injection of an adenoviral vector expressing IL-12 demonstrated minimal reduction in transfer efficiency.[25] Despite the generation of increased antiadenoviral antibody titers to SCH 58500 in all treated patients, we were also able to demonstrate transgene expression after multiple cycles of dosing. There was no obvious enhanced transgene expression in the two individuals who were treated at level 1 because of no demonstrable adenoviral immunity. Not all patients underwent sampling with each cycle of treatment, due to the invasive nature of laparoscopy. Nonetheless, our data clearly show the presence of transgene expression in RNA isolated from both ascitic fluid and tumor biopsies. The alternative explanation of persistent, stable expression of SCH 58500 over time is inconsistent with *in vitro* and *in vivo* preclinical observations.

For a single case, *in situ* PCR data confirmed gene transfer in tumor cells obtained at laparoscopic biopsy. It is not possible to determine the percent of tumor cells transduced because of variability in the size of the biopsies obtained and the variation in the depth of SCH 58500 penetration. For example, in the case of a 3-mm biopsy with 1 mm of penetration and 100% transduction to the level of penetration, one might infer 33% transduction efficiency. However, because the size of the lesion is unknown, the true transduction efficiency cannot be calculated. Similarly, a smaller (2 mm) biopsy from the same site would provide a different estimate of transduction efficiency. This important parameter cannot be estimated nearly as well in human clinical trials as it can be in cell culture, or in orthotopic animal models with smaller and more uniform lesions. Further *in situ* PCR studies are ongoing and will be the subject of a separate report (S Wen et al, in preparation).

Several investigators have postulated that adenoviral transfection efficiency is determined by the presence of coxsackie viral receptor (CAR) on the surface of epithelial cells.[64,65] We did not have sufficient samples to test this hypothesis as an explanation for the failure to achieve transfection in all samples collected or the differential

expression of transgene, which varied between barely detectable to 89,000 copies/per copy of β-actin. Variations in CAR receptor levels, however, may explain differences in transfection efficiency between ovarian cancer cell lines transduced with SCH 58500 *in vitro*.[66]

The inclusion of a subset of patients who received multiple courses of SCH 58500, both alone and in combination with chemotherapy, provided the opportunity not only to compare cumulative toxicity but also to gain preliminary data relevant to clinical response. As we have demonstrated, the combination of SCH 58500 with conventional chemotherapy for ovarian cancer added little to the toxicity of SCH 58500 alone. The frequent appearance of new CT-measurable lesions during the course of treatment with SCH 58500 accompanied by concomitant dramatic decreases in CA125 suggests that for gene replacement studies utilizing adenoviral vectors, CT scans are not a valid means to assess response. Also supporting this conclusion is the observation of mixed clinical responses observed in the same individual with objective responses of some lesions accompanied by the simultaneous development of new lesions in the same individual. Fortunately, other studies have demonstrated that CA125 responses to ovarian cancer treatment correlate very well with CT responses when CT is a valid measure of response.[41,42] Because CA125 responses also correlate well with overall survival,[67-70] they should not be dismissed out of hand. Indeed, because inflammatory changes in the peritoneal cavity may effect modest elevations of CA125 independent of ovarian cancer,[71-74] the interpretation of the overall responses in this study solely on the basis of CA125 response in the face of extensive inflammation, may actually serve to underestimate true response rates. The number of CA125 responders and the degree of response observed in groups 2 and 3 is remarkable based on the heavily pretreated nature of these patients. These data suggest that SCH 58500 has no negative impact on clinical outcome expected from standard chemotherapy treatments. Finally, it should also be noted that our multiple-dose cohort contained bulky tumor deposits, not the most optimal group to study i.p. regimens of any type.[75] We conclude that SCH 58500 is safe, well tolerated, and in combination with platinum-based chemotherapy provides response data to justify its further clinical testing for efficacy in the newly initiated phase III trial for front-line treatment of minimal residual ovarian cancer after primary surgical cytoreduction.

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Successful Adenovirus-Mediated Wild-Type *p53* Gene Transfer in Patients With Bladder Cancer by Intravesical Vector Instillation

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Purpose: **To study safety, feasibility, and biologic activity of adenovirus-mediated *p53* gene transfer in patients with bladder cancer.**

Patients and Methods: **Twelve patients with histologically confirmed bladder cancer scheduled for cystectomy were treated on day 1 with a single intratumoral injection of SCH 58500 (rAd/p53) at cystoscopy at one dose level (7.5×10^{11} particles) or a single intravesical instillation of SCH 58500 with a transduction-enhancing agent (Big CHAP) at three dose levels (7.5×10^{11} to 7.5×10^{13} particles). Cystectomies were performed in 11 patients on day 3, and transgene expression, vector distribution, and biologic markers of transgene activity were assessed by molecular and immunohistochemical methods in tumors and normal bladder samples.**

Results: **Specific transgene expression was detected in tissues from seven of eight assessable patients treated with intravesical instillation of SCH 58500 but in none of three assessable patients treated with intratumoral injection of SCH 58500. Induction of RNA and protein expression of the p53 target gene *p21/WAF1* was demonstrated in samples from patients treated with SCH 58500 instillation at higher dose levels. Distribution studies after intravesical instillation of SCH 58500 revealed both high transduction efficacy and vector penetration throughout the whole urothelium and into submucosal tumor cells. No dose-limiting toxicity was observed, and side effects were local and of transient nature.**

Conclusion: **Intravesical instillation of SCH 58500 combined with a transduction-enhancing agent is safe, feasible, and biologically active in patients with bladder cancer. Studies to evaluate the clinical efficacy of this treatment in patients with localized high-risk bladder cancer are warranted.**

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AN ESTIMATED 261,000 new cases of bladder cancer are diagnosed worldwide per year. Bladder cancer is prevalent in the developed countries, where it affects mainly men and is frequently associated with a history of tobacco smoking or some occupational exposures, and in Northern Africa and Western Asia, where it is related to endemic infection with the parasite *Schistosoma mansonii*.[1] In the Western world, 70% to 80% of patients present with superficial bladder tumors, which can be treated with transurethral resection.[2,3] However, patients with less differentiated, large or multilocular bladder tumors as well as patients with carcinoma in situ or stage I bladder cancer are at high risk for tumor recurrence and development of muscle-invasive disease or distant metastases.[4,5] Treatment strategies for such high-risk patients include local resection with close surveillance,[2] local resection and intravesical therapy using bacillus Calmette-Guerin or cytotoxic agents,[6-8] or radical cystectomy with urinary diversion or reconstructive surgery.[9,10] Radical cystectomy provides optimal control of the bladder tumor, but at the price of organ loss. Intravesical and systemic medical therapies have substantial toxicities and bear the risk of local recurrence or tumor progression. Thus, new bladder-preserving treatment options for high-risk bladder cancer are required.

Mutations of the *p53* tumor suppressor gene are the most common genetic alteration in human cancers.[11] The role of p53 in the prevention of oncogenic transformation, maintenance of genetic stability, and sensitivity to commonly used cancer treatments is well established.[12,13] In some but not all studies, nuclear accumulation of p53 as an indicator for mutations in the p53 DNA binding domain was associated with an adverse prognosis in patients with bladder cancer.[14-17] Hence, somatic gene transfer of the *p53* tumor suppressor is an attractive new treatment modality for malignant bladder tumors. Preclinical cancer models have

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demonstrated that the expression of *p53* by viral or nonviral gene transfer technology effectively induced apoptosis or sensitized cancer cells to drug- or radiation-induced cell death.[18] These results have fostered the translation of *p53* gene therapy into early clinical studies, which were conducted in patients with advanced lung, head and neck, ovarian, or liver cancers.[19-23] Using intratumoral injection of adenoviral[20-22,24] or retroviral[19] *p53* expression vectors, local transgene expression[20,22] and evidence for local tumor regressions and induction of apoptosis[19,24] were reported from several phase I and pilot studies. However, the only controlled phase II study in patients with newly diagnosed advanced non–small-cell lung cancer (NSCLC) failed to demonstrate a significant clinical benefit from local *p53* gene transfer by intratumoral vector injection in combination with an effective first-line chemotherapy.[25] One reason for this apparent clinical inactivity might be insufficient gene delivery and transduction after intratumoral injection of adenoviral *p53* expression vectors. Systematic studies of these important parameters, however, are absent in cancer patients.

One way to overcome the potential limitations of the intratumoral injection approach is the instillation of high-vector doses into cavitary organs, such as the pleural space,[26] peritoneal cavity, or bladder. This should allow a homogeneous vector distribution along the tumor surfaces, as opposed to a vector distribution along the track of an injection needle. Preclinical studies have demonstrated the feasibility of this approach and have highlighted the importance of the addition of transduction-enhancing agents to maximize transgene expression in the bladder.[27,28]

To address this hypothesis, a study of safety, feasibility, and biologic activity of an intravesical instillation or an intratumoral injection of an adenoviral expression vector encoding wild-type p53 (SCH 58500) was conducted in patients with invasive bladder cancer. To allow assessment of vector distribution, transgene expression, and induction of p53 target genes or additional markers of biologic activity after the study treatment, only patients scheduled for radical cystectomy were enrolled onto this trial, enabling extensive tissue sampling for these analyses.

PATIENTS AND METHODS

Patients

Adult patients with histologically confirmed, muscle-invasive bladder cancer and indication for radical cystectomy were eligible for enrollment. Additional inclusion criteria were a life expectancy of at least 3 months, a Karnofsky performance score of at least 70%, and the absence of any clinical or laboratory evidence (WBC count $\geq$ 3,000/μL, absolute neutrophil count $\geq$ 1,000/μL, platelet count $\geq$ 100,000/μL, creatinine $<$ 1.5 mg/dL, bilirubin $<$ 1.5 mg/dL, AST and ALT $<$ 1.5 times the upper limit of normal, and prothrombin and partial thromboplastin times within normal limits) for dysfunction of the hematopoietic, liver, renal, or coagulation systems. An interval of at least 4 weeks between prior chemotherapy, radiation, or major surgery was mandatory. Pregnant or nursing women, fertile women not practicing medically accepted contraception, patients with uncontrolled serious bacterial, fungal, or viral infections, human immunodeficiency virus–positive patients, and immunosuppressed patients were not eligible. Molecular or immunohistochemical evidence for an intratumoral *p53* mutation was not required for eligibility. All patients provided written informed consent. After written informed consent, control tissue samples were obtained from patients with advanced bladder cancer or patients with nonmalignant bladder disease treated by cystectomy.

Study Design

This was an open-label, single-center, phase I dose-escalation study of a single intratumoral injection (part A) or a single intravesical instillation (part B) of SCH 58500 (rAd/p53). Three patients were treated at each dose level, and dose escalation proceeded if no dose-limiting toxicity was observed. A dose-limiting toxicity was defined as any World Health Organization (WHO) grade 4 toxicity or any WHO grade 3 toxicity lasting more than 1 week. Adverse events that were clearly related to cystoscopy, catheter placement, cystectomy, or palliative treatment to the tumor were not considered dose-limiting. The protocol was approved by the local ethics committee (Bezirksärztekammer Rheinhessen) and the National Regulatory Office (Kommission Somatische Gentherapie der Bundesärztekammer). The study was conducted according to the Declaration of Helsinki (amended version, Hong Kong, 1989) and following the principles of good clinical practice.

Study Treatments

SCH 58500 is a replication-defective recombinant adenoviral vector encoding the complete human wild-type *p53* cDNA.[20,29] Doses were 7.5×10^{11} particles in level 1, 7.5×10^{12} particles in level 2, and 7.5×10^{13} particles in level 3. Patients treated in part A received a single intratumoral injection of 1 mL SCH 58500 in a standard saline-based solution[20] at cystoscopy on day 1. Patients treated in part B received a single intravesical instillation (total volume, 120 mL) of SCH 58500 in 20 mg/mL solution of Big CHAP, a transduction-enhancing agent,[28] through a transurethral catheter on day 1. After instillation, the catheters were blocked to allow a contact time of 60 minutes, followed by release of the catheter and extensive bladder irrigation with saline. During the course of the study, the vector instillation was divided into two sequential administrations of 50% of the vector dose each. The planned contact time for each half dose was 30 minutes; the second instillation immediately followed the release of the first dose. After treatment, all patients were hospitalized in single rooms in a biosafety environment at the study center for at least 24 hours or until adenovirus shedding was no longer detectable. Approximately 48 hours after vector administration (day 3), all patients underwent routinely scheduled radical cystectomies, which were not part of the study treatment.

Study End Points

The primary objective of this study was to assess the safety, feasibility, and toxicity of a single dose of SCH 58500 administered by intratumoral injection (part A) or by intravesical instillation (part B) in patients with invasive bladder cancer. Secondary end points were to

Table 1. Sequences of the Oligonucleotide Primers and Probes Used in Real-Time RT-PCR Assays

Target Gene	Function	Sequence	Expected PCR Product Size (bp)
p21/WAF1	Forward primer	TGGAGACTCTCAGGGTCGAAA	65
	Reverse primer	GGCGTTTGGAGTGGTAGAAATC	
	Probe	CGGCGGCAGACCAGCATGAC	
SCH 58500	Forward primer	AACGGTACTCCGCCACC	94
DNA and RNA	Reverse primer	CGTGTCACCGTCGTGGA	
	Probe	CAGCTGCTCGAGAGGTTTTCCGATCC	
GAPDH	Forward primer	GAAGGTGAAGGTCGGAGTC	226
	Reverse primer	GAAGATGGTGATGGGATTTC	
	Probe	CAAGCTTCCCGTTCTCAGCC	

NOTE. All of the probes were labeled with the reporter signal FAM and TAMRA as the quencher.

assess vector distribution in normal and malignant bladder tissue, transgene expression, and markers of biologic activity in samples obtained at cystectomy.

Clinical Monitoring

Patients were closely monitored for adverse events for the first 7 days after study treatment. After hospital discharge, the patients were followed bimonthly for 1 year at the study center. The monitoring for the first 7 days after treatment included assessment of clinical symptoms, physical examination, monitoring of vital signs, Karnofsky index, concomitant medication, and recording of adverse events. Hematology, serum chemistry, and urinalysis were performed before treatment and on days 1, 2, 4, and 6 and during follow-up visits.

Virology Studies

Adenovirus shedding was monitored in urine, stool, or rectal swab specimens by means of a qualitative enzyme-linked immunosorbent assay (ELISA) before treatment on days 2 and 3 and until no adenovirus shedding was detectable.[20] In addition, urine samples were collected at multiple time points after study treatment and were examined for the presence of infectious adenoviruses by a flow cytometry–based infectivity assay.[30]

Detection of SCH 58500 DNA and Expression of Transgenic p53, p21/WAF1, *and the Coxsackie and Adenovirus Receptors*

SCH 58500 virus DNA, vector-specific transgene expression, p53 target gene *p21/WAF1* expression,[31,32] and Coxsackie and adenovirus receptor (CAR) expression were assessed in tumor samples and normal bladder tissue obtained at cystectomy by reverse transcriptase polymerase chain reaction (RT-PCR), as described previously,[20] and quantitative real-time PCR,[33,34] as described previously.[35] In brief, DNA and RNA were coextracted from frozen bladder samples using Trireagent (Molecular Research Center, Cincinnati, OH). Extracted RNA was DNased, and PCR was performed to ensure no DNA contamination. Real-time quantitative PCR and RT-PCR were performed using the ABI 7700 sequence detector (Applied Biosystems, Foster City, CA). The *GAPDH* gene was used as an internal control to assess the quality of assay samples. Gene expression results were expressed as number of copies per 1,000 copies of *GAPDH*. SCH 58500 DNA was quantified by comparison to viral DNA extracted from purified SCH 58500 virus (Qiagen, Valencia, CA). cRNAs were used as standards to quantify *p53, p21,* and *GAPDH* gene expression. The sequences of the oligonucleotide primers and probes are listed in Table 1. Primers for SCH 58500 gene and its expression were designed specifically to amplify SCH 58500 but not the human *p53* gene. Whenever possible, assays were performed on at least two different samples of tumor or nontumor tissue per patient. Bladder tissue samples obtained from patients with advanced bladder cancer not treated with SCH 58500 served as negative controls. A cutoff level for positive real time PCR samples was set as the detection of at least 10 copies per reaction.[35]

Analysis of Tissue Sections

Localization of SCH 58500 was assessed using a direct in situ PCR method.[36] Formalin-fixed paraffin-embedded tissues were cut into 5-μm sections, placed on in situ PCR slides, and baked for 2 to 3 hours at 60°C on a slide hot plate. The slides were washed in xylene to remove the paraffin, followed by an incubation with 0.02 N HCl and digestion with 2.5 μg/mL proteinase K (Qiagen) at 37°C for 30 minutes. The endogenous alkaline phosphatase activity was eliminated by incubating the slides in ice-cold 20% (vol/vol) acetic acid. Slides were dehydrated in graded alcohols and rehydrated in 45 μL of PCR master mix containing 1 μmol/L of each dinitro-phenyl (DNP)-labeled primer, 200 μmol/L of each dNTP, 2.5 mmol/L magnesium chloride, and 10 units of AmpliTaq DNA polymerase (Applied Biosystems). Primers were designed to amplify a SCH 58500-specific sequence located between the cytomegalovirus promoter (5'-CGTGTCAC-CGTCGTGGA-3') and the upstream *p53* cDNA (5'-CCACTGCT-TACTGGCTTATCGAAAT-3'). This primer selection prevents the amplification of genomic *p53* DNA.[29] Reactions were performed in a Perkin Elmer Gene Amp In Situ PCR System 1000 (Applied Biosystems) programmed for one cycle of denaturation at 95°C for 5 minutes and annealing at 55°C for 90 seconds, followed by 34 cycles of 94°C for 30 seconds and 55°C for 90 seconds. After completion of the PCR, slides were washed two times with standard saline citrate (0.3 mol/L NaCl and 0.03 mol/L sodium citrate) and blocked with casein solution (Vector, Burlingame, CA). For tissue sections, the DNP molecules incorporated into the PCR amplicons were detected using an anti-DNP antibody conjugated with alkaline phosphatase (Applied Biosystems). The sections were stained using the alkaline phosphatase substrate NBT/BCIP (nitro-blue tetrazolium/5-bromo-4-chloro-3-indolyl phosphate) (Boehringer Mannheim, Germany) and then counterstained with Nuclear Fast Red (Vector). As a negative control, each section was processed, but the PCR reaction was performed without AmpliTaqDNA polymerase. Samples from rat bladders instilled with SCH 58500 or a *β-galactosidase*–expressing adenoviral vector (Ad5.β-gal) served as positive and negative controls.

Table 2. Patient Demographics, Tumor Stages, Histologies, and Transgene Expression After SCH 58500 Treatment

Patient No.	Age (years)	Sex	Histology	p53	Stage	Study Group	RT-PCR
001	68	Male	TCC	0	pT4aN2M0 G4	A1	–
002	37	Female	SCC	2	pT3bN0M0 G2-3	A1	–
003	64	Male	TCC	1	pTaN0M0 G2-3	A1	–
004	69	Male	TCC	3	pT1N0M0 G2	B1	+
005	69	Male	TCC	1	pT3aN0M0 G2	B1	+
006	73	Male	TCC	0	pT3aN0M0 G2	B1	+
007	69	Male	TCC	1	pTisN0M0 G3	B2	+
008	69	Male	SCC	3	pT3aN0M0	B2	–
009	70	Male	TCC	0	pT1N0M0 G3	B2	+
010	60	Female	TCC	1	pT1N1M1	B3	ND
011	84	Male	TCC	1	pT2bN1M0 G3	B3	+
012	82	Male	TCC	2	pT4N0M0 G3	B3	+

Abbreviations: TCC, transitional cell carcinoma; SCC, squamous cell carcinoma; Stage, tumor stage according to tumor-node-metastasis classification; p53, immunohistochemical detection of nuclear p53 expression in baseline tumor biopsies in < 10% of tumor cells = 0, 11%-25% of tumor cells = 1, 26%-50% of tumor cells = 2, > 50% of tumor cells = 3; A1, intratumoral injection (part A), dose level 1 (7.5×10^{11} particles); B1, intravesical instillation (part B), dose level 1 (7.5×10^{11} particles); B2, intravesical instillation, dose level 2 (7.5×10^{12} particles); B3, intravesical instillation, dose level 3 (7.5×10^{13} particles); RT-PCR, positive (+) or negative (−) expression of vector-specific *p53* RNA as detected by RT-PCR analysis of samples obtained at cystectomy; ND, not determined (no cystectomy performed).

The protein expression of p53, *p21/WAF1*, apoptosis-related and cell cycle–related genes, and CAR was assessed by immunohistochemistry in formalin-fixed paraffin-embedded tissue sections. Primary antibodies against p53 (M7001, Dako Diagnostika, Hamburg, Germany), *p21/WAF1* (M7202, Dako), Bcl-2 (M0887, Dako), Bak (AM04, Calbiochem, San Diego, CA), Bax (Ab-1/PC66, Calbiochem), MIB1 (dia 505, Dianova, Hamburg, Germany), and CAR (a gift from Dr Robert W. Finberg, Dana-Farber Cancer Institute, Boston, MA[37,38]) were used. Apoptotic cells were visualized by microscopy following the terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate-biotin nick end-labeling (TUNEL) method[39] and by means of laser scanning cytometry, as previously described.[40] Normal bladder and tumor tissue samples from patients not treated with SCH 58500 served as controls.

RESULTS

Enrollment and Treatments

Twelve patients from a single center were enrolled onto the study. Baseline characteristics and histologies of the study patients are listed in Table 2. Three patients were treated at dose level 1 in part A (intratumoral injection) of the study. No additional dose escalation was performed in part A. Nine patients were treated at three different dose levels in part B (intravesical instillation). Eleven patients underwent radical cystectomies after study treatment. In one patient, the tumor was determined to be unresectable with curative intent at laparotomy. Thus, tumor samples for assessment of the secondary end points were obtained from 11 patients treated with SCH 58500 at three dose levels.

Toxicity

Postoperatively, one patient treated in part A suffered from WHO grade 1 fatigue. No toxicities were observed in the other two patients treated with intratumoral injection at cystoscopy. The predominant toxicities observed in patients treated in part B of the study were urethral and vesical burning, which reached WHO grade 2 in two patients and WHO grade 3 in another two patients. In addition, one patient each experienced WHO grade 2 and grade 3 abdominal pain. These symptoms were relieved in two patients treated at dose level 1 by a reduction of the contact time, for which the transurethral catheters were clamped. Hence, for patients treated at dose levels 2 and 3, the treatment was administered in two sequential 30-minute sessions. Additionally, patients treated at dose level 3 were premedicated with 50 mg of pethidine and 20 mg of butylscopolamine. Despite these modifications, the planned contact time had to be reduced by several minutes in three patients treated at dose level 2 and in one patient treated at dose level 3. All symptoms resolved immediately after release of the transurethral catheter and bladder irrigation with saline. No fever, chills, or other signs of systemic toxicity were observed in patients treated in part B. No alterations of laboratory parameters, including liver enzymes and bilirubin, were detected before surgery on day 3. Three patients were hospitalized because of fever of unknown origin within 4 to 6 weeks after surgery and quickly recovered under treatment with broad-spectrum antibiotics. In one of these patients, a methicillin-resistant *Staphylococcus aureus* was isolated from a catheter. Thus, even at the highest dose level of 7.5×10^{13} particles SCH 58500 administered by intravesical instillation, no dose-limiting toxicities were observed.

Transgene Expression and Biologic Activity

In two of three assessable patients treated in part A (intratumoral injection), vector DNA was found by PCR

Table 3. Induction of p21/WAF1 RNA and Protein Expression After Intravesical SCH 58500 Treatment

Patient No.	Study Group	Normal Bladder Tissue		Tumor Tissue	
		p21 RNA	p21 IHC	p21 RNA	p21 IHC
Controls	—	1.08 ± 1.8	—	0.26 ± 0.38	—
004	B1	3.5 ± 2.2	0/0	0.92 ± 1.12	0/2
005	B1	2.47	0/0	1.16 ± 1.37	0/2
006	B1	.57 ± 0.4	0/0	1.16 ± 1.43	0/0
007	B2	2.62	0/0	0.32 ± 0.29	0/0
008	B2	ND	0/0	0.32 ± 0.29	0/0
009	B2	4.59	0/0	0.61	0/0
010	B3	ND	ND	ND	ND
011	B3	1.29 ± .42	0/0	10.4 ± 20.69	0/2
012	B3	2.66 ± 1.56	0/0	3.99 ± 4.7	0/1

Abbreviation: ND denotes not determined (insufficient sampling or no cystectomy performed).

NOTE. Tissue samples from bladder tumors and normal bladder tissue obtained at cystectomy were examined by real-time RT-PCR (p21 RNA) and immunohistochemistry (p21 IHC). Normal bladder samples from four patients and tumor samples from five patients not treated with SCH 58500 served as controls for real-time RT-PCR (Controls). Results from real-time RT-PCR are expressed as mean ± SD × 10,000 copies normalized to 1,000 copies *GAPDH* RNA. Results from immunohistochemistry are presented as nuclear expression of p21/WAF1 in biopsies before and after SCH 58500 treatment (< 10% of tumor cells = 0; 11%-25% of tumor cells = 1; 26%-50% of tumor cells = 2; > 50% of tumor cells = 3).

analysis of posttreatment tumor samples (not shown). However, no transgene expression as assessed by RT-PCR analysis of vector-specific *p53* expression was detected after intratumoral injection of SCH 58500 at cystoscopy (Table 2). In contrast, vector-specific *p53* transgene expression was found by RT-PCR analyses of tissue samples from seven of eight assessable patients treated with intravesical instillation of SCH 58500 (Table 2).

To address whether the *p53* transgene expression translated into biologic activity, we determined the quantitative expression of the p53 target gene *p21/WAF1* by real-time RT-PCR analysis of tumor and normal bladder samples from patients treated with intravesical instillation of SCH 58500 or untreated control patients. The *p21/WAF1* expression in tumor samples from untreated control patients was lower than in normal bladder samples (Table 3). Assaying nontumor bladder samples from patients treated with SCH 58500 instillation, moderate changes in *p21/WAF1* expression were detected when compared with untreated controls (Table 3). However, in tumor samples from patients treated at the highest dose level of 7.5×10^{13} particles SCH 58500 *p21/WAF1*, expression was increased up to 40-fold compared with control tumor samples from patients not receiving gene therapy (Table 3). Immunohistochemical analyses revealed an increased *p21/WAF1* protein expression after SCH 58500 treatment in tumor tissues but not in normal bladder samples from four patients with undetectable or low *p21/WAF1* protein expression at baseline (Table 3). No significant correlation between transgene expression, *p21/WAF1* induction, and CAR expression, as determined by RT-PCR analysis and immunohistochemistry, could be established. However, the CAR expression detected by immunohistochemistry exhibited a considerable heterogeneity among tumors from different patients as well as among different regions of the same tumor (not shown). Immunohistochemical analyses of p53 expression or expression of additional apoptosis-related or cell cycle–related genes revealed no consistent changes in relation to SCH 58500 treatment. Moreover, we failed to detect a significant induction of apoptosis as assessed by TUNEL staining and microscopy or laser scanning microscopy in samples taken at cystectomy approximately 48 hours after SCH 58500 treatment (not shown).

Taken together, these data demonstrate that a detectable p53 transgene expression in bladder tumors can be achieved by intravesical instillation of SCH 58500 in combination with a transduction-enhancing agent. At the highest dose level of 7.5×10^{13} particles SCH 58500, evidence for biologic activity in terms of RNA and protein expression of the p53 target gene *p21/WAF1* was obtained.

Vector Distribution

Using quantitative real-time PCR, SCH 58500 DNA copies were detected in normal bladder and tumor samples from patients treated with intravesical instillation in a dose-dependent manner, whereas no SCH 58500 DNA was found in samples from control patients not treated with SCH 58500 (Fig 1). The demonstration of vector DNA or transgene expression in tissue homogenates does not provide information regarding the transduction efficacy or the vector penetration. Therefore, tissue sections from patients treated in part B were analyzed by in situ PCR, revealing a strong vector-specific signal throughout the whole urothelium (Fig 2). Moreover, SCH 58500 DNA was also detected

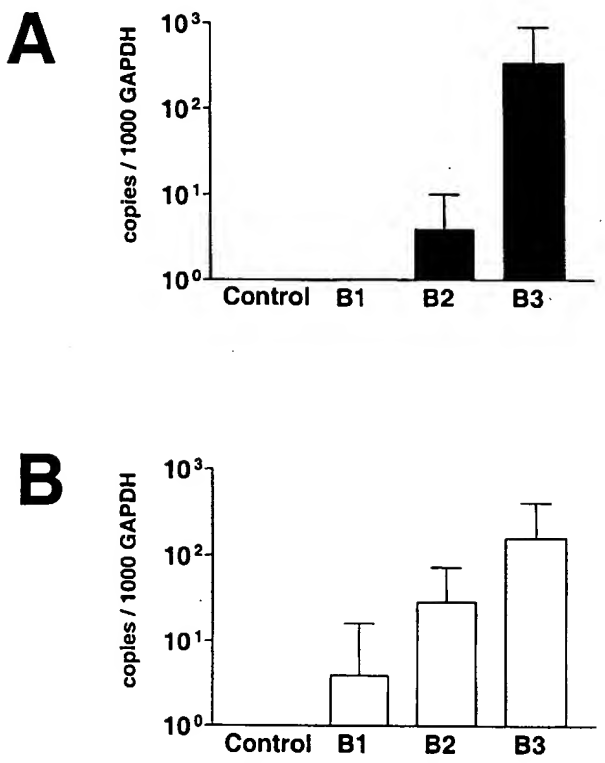

Fig 1. Quantitative detection of SCH 58500-specific DNA sequences (mean ± SD) by real-time PCR analysis of samples from tumor (A) and nontumor bladder tissue (B) of untreated bladder cancer patients (control) and patients treated with intravesical instillation of SCH 58500 at dose levels 1 (B1), 2 (B2), and 3 (B3).

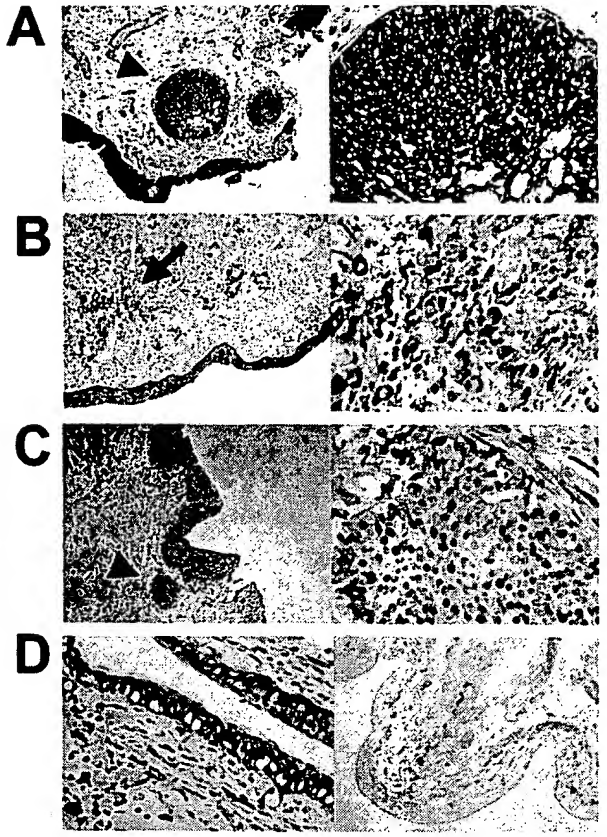

Fig 2. SCH 58500 vector distribution (in situ PCR) in tissue sections from patient no. 011 (A and B) and patient no. 005 (C) treated with intravesical instillation. Arrowheads indicate submucosal tumor nodules (A and C); arrow indicates cells in the Lamina propria (B). Sections from rat bladders injected with SCH 58500 (D, left panel) or control virus (D, right panel) are shown as positive and negative controls.

in submucosal tumor nodules as well as in cells in the Lamina propria. Thus, intravesical instillation of SCH 58500 in combination with a transduction-enhancing agent can achieve an uniform vector penetration throughout the urothelium as well as into submucosal tumor tissues.

Virologic Studies

After SCH 58500 treatment, all patients in both study groups underwent extensive bladder irrigation with 6 L saline through a transurethral catheter over a period of 36 to 48 hours. Excretion of infectious adenoviruses was detected by a sensitive flow cytometry-based assay[30] in samples taken from the first 2 to 4 L of void volume. No detectable urinary adenovirus excretion was found after 6 L of bladder irrigation (Fig 3). None of the urine samples taken 24 hours after study treatment gave a positive result in the qualitative on-site ELISA assay (not shown).

Long-Term Follow Up

Nine of the 12 study patients were alive at a median follow-up of 30 months. In addition to SCH 58500 treatment and radical cystectomy, two patients received a platinum-based adjuvant chemotherapy regimen. In one patient treated in part A, fulminant liver metastases developed 4 weeks after surgery, which were not detectable on computed tomogram and ultrasound examinations performed at the preoperative staging. The patient was treated with palliative chemotherapy, but he died from progressive liver failure 7 weeks after cystectomy. One patient treated in part A developed a *Mycoplasma* pneumonia during adjuvant chemotherapy. In total, three patients died from disease progression, and one patient is being treated with palliative chemotherapy for recurrent disease.

DISCUSSION

A major challenge in the conservative management of localized bladder cancer is the frequent recurrence and progression to an advanced tumor stage in patients with high-risk tumors.[2] To improve disease control, local tumor

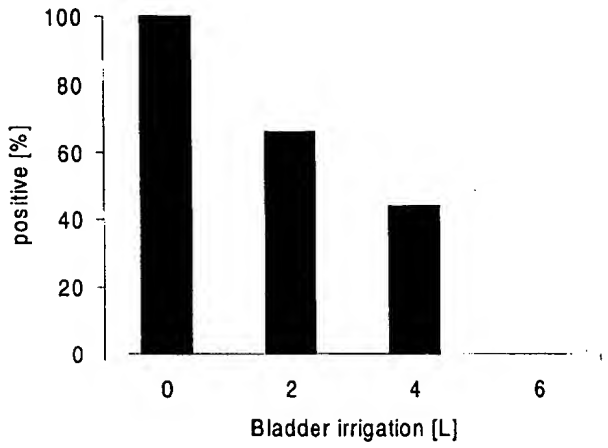

Fig 3. Excretion of infectious adenoviruses after intravesical SCH 58500 treatment. The percentage of patients (n = 12) with urine samples positive for infectious adenoviruses after the indicated volumes of bladder irrigation with saline.

resection is combined with intravesical therapy with bacillus Calmette-Guerin or anticancer agents.[8] However, these treatments have a substantial toxicity and may reduce the risk of recurrences but do not prevent disease progression.[6,7] Thus, new treatment options for high-risk superficial bladder cancer are required. Mutations of the *p53* tumor suppressor gene are frequently found in bladder cancer, are associated with an adverse prognosis in some studies, and may contribute to a more aggressive clinical course and resistance to anticancer treatment.[14,15] In an ortopic injection model of bladder cancer, *p53* gene transfer acted synergistically with cisplatin to prevent tumor growth and induce apoptosis in vivo.[41]

In the present phase I study, we tested whether adenoviral vector-mediated wild-type *p53* gene transfer is safe, feasible, and biologically active in patients with invasive bladder cancer. Taking advantage of the anatomy of the bladder, we planned to evaluate two different modes of vector administration: the intratumoral injection of vector solution, because it has been performed in several clinical studies of cancer gene therapy,[19-21] and the intravesical vector instillation via a transurethral catheter. Because preclinical studies convincingly demonstrated that the transduction efficacy of adenoviral vectors instilled into the bladder can be dramatically enhanced by the addition of several compounds,[27,28] here we administered intravesical SCH 58500 in combination with the transduction-enhancing agent Big CHAP.[28] Both modes of administration of the study treatment, intratumoral injection at cystoscopy and transurethral intravesical instillation, were well tolerated and devoid of any detectable systemic toxicity. Successful gene transfer after intravesical instillation of SCH 58500 in combination with Big CHAP was detected by RT-PCR analysis in seven of eight assessable patients. Moreover, evidence for biologic activity of the transgene, as determined by quantitative RT-PCR analysis of RNA expression as well as by immunohistochemical analysis of protein expression of the p53 target gene *p21/WAF1*,[32] was found in patients treated at higher dose levels. Transgene expression did not seem to correlate with the CAR expression status of the tumor samples as determined by RT-PCR analysis and immunohistochemistry. However, the relatively small number of patients enrolled onto this study and the detection methods for CAR expression might have influenced this result. Compared with the effective transduction achieved by intravesical vector instillation, no evidence for transgene expression was detected in the three patients treated by intratumoral injection of SCH 58500 at dose level 1, whereas SCH 58500 DNA sequences were detectable in two patients by PCR analysis. This was surprising, given that in a previous study in patients with NSCLC treated by intratumoral injection of SCH 58500, *p53* transgene expression was detected in four of five assessable patients receiving the same vector dose of 7.5×10^{11} particles.[20] Because intratumoral vector injection at cystoscopy is a relatively invasive procedure compared with transurethral vector instillation, it was decided not to proceed with the dose escalation in part A of this trial. Hence, we cannot exclude that at higher dose levels, a *p53* transgene expression in bladder tumors would have been achieved by intratumoral injection of SCH 58500 at cystoscopy. Furthermore, the addition of Big CHAP or other transduction-enhancing agents[28] might also be beneficial in the case of intratumoral vector injection in the bladder. However, in the light of the efficacy and ease of the intravesical instillation approach, intratumoral vector injection at cystoscopy clearly is the inferior approach for vector administration in bladder cancer.

In contrast to the results obtained with the p53 target gene *p21/WAF1*, we found no consistent changes in the expression of *p53*, various cell cycle–related or apoptosis-related genes, or TUNEL staining in response to SCH 58500 administration. This observation might be limited by the small number of patients enrolled onto the trial and the availability of only a single time point for these examinations. Moreover, the activity of many genes regulating apoptosis is not controlled by their expression level but by conformational changes or changes in their subcellular localization,[42] which cannot be detected by the methods applied in this study. Nevertheless, the *p21/WAF1* response is a valid marker for biologic activity of transgenic p53,

which has been confirmed in additional settings of clinical p53 gene therapy.[35,43]

In addition to molecular and immunohistochemical evidence for transgene expression and biologic activity, important information related to the vector distribution throughout the bladder and vector penetration into tumor tissues was gathered from this trial. We demonstrated by quantitative PCR analysis that administration of higher particle doses resulted in the recovery of higher copy numbers of SCH 58500-specific DNA from tissue samples (Fig 3). This was not unexpected; however, it suggests that together with the evidence for increased *p21/WAF1* expression at high doses, a plateau of the biologic activity was not reached by the intravesical instillation of 7.5×10^{13} particles SCH 58500. Presently, technical limitations preclude the administration of a more concentrated adenovirus solution, leaving this issue unresolved. With respect to the vector distribution after intravesical instillation, we found a uniform distribution of SCH 58500 DNA throughout the normal urothelium and the luminal tumor tissues by in situ PCR analysis of bladder sections. Moreover, vector DNA could also be found in apparently submucosal tumor nodules as well as in cells in the Lamina propria. These results confirm the hypothesis that the instillation approach results in an improved vector distribution. In addition, they demonstrate that even submucosal tumor cells can be targeted by the luminal administration of an adenovirus in combination with a transduction-enhancing agent in the bladder.

The optimal dosing schedule for intravesical SCH 58500 instillation remains to be established. Because of the procedure-associated discomfort observed in most patients treated in part B of this study, the contact times varied considerably. Yet SCH 58500 penetration and transgene expression analyses yielded promising results. It seems likely that even shorter contact times than the ones allowed in the course of this trial might result in sufficient transduction rates with lower local toxicity, a hypothesis supported by initial data from preclinical in vivo models. The intravesical instillation of SCH 58500 through a transurethral catheter also is environmentally safe, because infectious adenoviruses excreted in the urine after SCH 58500 treatment can easily be recovered in a contained system. The virologic studies performed in this trial suggest that if the bladder is sufficiently irrigated, infectious viral particles are only excreted with the first 4 L of irrigation fluid. This could minimize hospitalizations and could even allow outpatient treatment.

The design of the present phase I study precluded the collection of data regarding the long-term effects of the intravesical administration of such high-vector doses as well as signs for clinical efficacy. However, important and unique data demonstrating effective vector distribution, transgene expression, and biologic activity after a clinically practicable and safe gene transfer procedure were obtained in patients with invasive bladder cancer. These results provide a strong rationale for future investigation of adenovirus therapy in bladder cancer and support trials addressing the clinical efficacy of intravesical SCH 58500 treatment in patients with superficial high-risk bladder cancer.

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